Court File No. 98-CV-141369 CP00

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N :

DIANNA LOUISE PARSONS, deceased by her Estate Administrator, William John Forsyth, MICHAEL HERBERT CRUICKSHANKS, DAVID TULL, MARTIN HENRY GRIFFEN, ANNA KARDISH, ELSIE KOTYK, Executrix of the Estate of Harry Kotyk, deceased and ELSIE KOTYK, personally

Plaintiffs

and

THE CANADIAN RED CROSS SOCIETY, HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO and THE ATTORNEY GENERAL OF CANADA

Defendants

and

HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF ALBERTA HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF SASKATCHEWAN, HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF MANITOBA, HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NEW BRUNSWICK HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF PRINCE EDWARD ISLAND, HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NOVA SCOTIA HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NEWFOUNDLAND, THE GOVERNMENT OF THE NORTHWEST TERRITORIES, THE GOVERNMENT OF NUNAVUT and THE GOVERNMENT OF THE YUKON TERRITORY

Intervenors

Proceeding under the *Class Proceedings Act, 1992*

Court File No. 98-CV-146405

B E T W E E N:

JAMES KREPPNER, BARRY ISAAC, NORMAN LANDRY, as Executor of the Estate of the late SERGE LANDRY, PETER FELSING, DONALD MILLIGAN, ALLAN GRUHLKE, JIM LOVE and PAULINE FOURNIER as Executrix of the Estate of the late PIERRE FOURNIER

Plaintiffs

and

THE CANADIAN RED CROSS SOCIETY, THE ATTORNEY GENERAL OF CANADA and HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Defendants

and

HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF ALBERTA, HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF SASKATCHEWAN, HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF MANITOBA, HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NEW BRUNSWICK, HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF PRINCE EDWARD ISLAND HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NOVA SCOTIA HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NEWFOUNDLAND, THE GOVERNMENT OF THE NORTHWEST TERRITORIES, THE GOVERNMENT OF NUNAVUT AND THE GOVERNMENT OF THE YUKON TERRITORY

Intervenors

Proceeding under the *Class Proceedings Act, 1992*

This is the 17th Affidavit
of Heather Rumble Peterson in the BC Action
and was made on October 13, 2017

No. C965349
Vancouver Registry

In the Supreme Court of British Columbia

Between:

Anita Endean, as representative plaintiff

Plaintiff

and:

**The Canadian Red Cross Society
Her Majesty the Queen in Right of the Province of
British Columbia, and The Attorney General of Canada**

Defendants

and:

**Prince George Regional Hospital, Dr. William Galliford,
Dr. Robert Hart Dykes, Dr. Peter Houghton, Dr. John Doe,
Her Majesty the Queen in Right of Canada, and
Her Majesty the Queen in Right of the Province of
British Columbia**

Third Parties

Proceeding under the *Class Proceedings Act*, R.S.B.C. 1996, C. 50

C A N A D A

PROVINCE OF QUÉBEC

DISTRICT OF MONTRÉAL

SUPERIOR COURT

Class action

NO : 500-06-000016-960

DOMINIQUE HONHON

Plaintiff

-vs-

THE ATTORNEY GENERAL OF CANADA
THE ATTORNEY GENERAL OF QUÉBEC
THE CANADIAN RED CROSS SOCIETY

Defendants

-and-

MICHEL SAVONITTO, in the capacity of the Joint Committee member for the province of Québec

PETITIONER

-and-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-and-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

C A N A D A

PROVINCE OF QUÉBEC

DISTRICT OF MONTRÉAL

SUPERIOR COURT

Class action

NO : 500-06-000068-987

DAVID PAGE

Plaintiff

-vs-

THE ATTORNEY GENERAL OF CANADA
THE ATTORNEY GENERAL OF QUÉBEC
THE CANADIAN RED CROSS SOCIETY

Defendants

-and-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-and-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

AFFIDAVIT OF HEATHER RUMBLE PETERSON
(Compensable HCV Drug Therapy)
Sworn October 13, 2017)

I, Heather Rumble Peterson, of the Town of Harrow, in the County of Essex, in the Province of Ontario, lawyer, SWEAR THAT:

1. I am a partner in the firm Strosberg Sasso Sutts LLP. I have assisted Harvey T. Strosberg, Q.C., counsel in action 98-CV-141369 and one of the Ontario court-appointed members of the Joint Committee, with all aspects of this action and the implementation and ongoing supervision of the 1986-1990 Hepatitis C Settlement Agreement ("Agreement") including the Transfused HCV Plan and the Hemophiliac HCV Plan (together, the "Plans") and as such have knowledge of the facts to which I now depose. Where I make statements in this affidavit which are not within my personal knowledge, I have identified the source of that information and belief. All of the information I am deposing to I do verily believe to be true.

Events Leading Up to this Application

2. Prior to the June 2016 joint hearings of the courts on allocating excess capital, the Joint Committee recognized that the 2013 medical model indicated a large number of class members would undergo treatment with direct-acting antiviral agents (DAAs) (with or without ribavirin or interferon), including those at Disease Level 2. The Joint Committee also recognized that, while the medical model provided for Disease Level 2 to Disease Level 3 transition based on disease progression, it did not account for Disease Level 2 to Disease Level 3 transition based on having taken or met a protocol for treatment with Compensable HCV Drug Therapy as provided for in the Plans.

3. Accordingly, the Joint Committee sought to ensure that the liabilities accounted for this and served motions requesting that the Courts declare that the amount of excess capital available for allocation was a lesser amount than originally determined, namely, $206,920,000.

4. The basis for the request for a reduction in excess capital was a belief on the part of the Joint Committee that an additional sufficiency liability in respect of Disease Level 2 claimants who are reclassified as Disease Level 3 claimants and become eligible for the $30,000 (1999 dollars) Disease Level 3 fixed payment based on taking or meeting a protocol for taking Compensable HCV Drug Therapy should be reflected in the financial position of the Trust.

5. The responding material served by the federal government included affidavit #4 of Peter Gorham attaching the Morneau Shepell *Actuarial Report on Proposed Allocation of the Actuarially Unallocated Funds as of 31 December 2013*. In that report, Mr. Gorham raised the issue of the appropriateness of Disease Level 2 to Disease Level 3 transition "by reason only of taking the new treatment…" Mr. Gorham suggested in his report that "the situation be reviewed to determine whether the court approved protocol regarding these payments should be revised."

6. The current motion/application seek to address this outstanding issue and one other issue in respect of Compensable HCV Drug Therapy.

The Relevant Provisions of the Plans and the Medical Evidence Protocol

7. The Plans provide for compensation triggered by class members reaching certain disease levels. The Agreement is progressive in nature in the sense that a class member can receive additional compensation if he or she progresses from one disease level to a higher level. The proposed HCV Late Claims Benefit Plan mirrors the Plans in this respect.

8. One of the ways that the Disease Level 3 requirement in section 4.01(1)(c) of the Plans is triggered relates to Compensable HCV Drug Therapy as it is defined in the Plans. Where class members have been treated with Compensable HCV Drug Therapy within the meaning of the Plans, or, have met or meet a protocol for Compensable HCV Drug Therapy (regardless of whether that treatment is recommended or taken) they are classified at Disease Level 3 and are eligible for a payment of $30,000 (indexed) under the Plans.

9. In addition, pursuant to section 4.05 of the Plans, class members who receive Compensable HCV Drug Therapy are entitled to be paid $1,000/month (indexed) for each completed month of such treatment.

10. Compensable HCV Drug Therapy is defined under the Plans as follows:

> "Compensable HCV Drug Therapy" means interferon or ribavirin, used alone or in combination, or any other treatment that has a propensity to cause adverse side effects and that has been approved by the Courts for compensation.
>
> **« médication indemnisable au titre du VHC »**, l'interféron ou la ribavirine, utilisé seul ou en combinaison, ou tout autre traitement qui est susceptible d'avoir des effets indésirables et que les tribunaux ont approuvé à des fins d'indemnisation.

11. In 2010, the Courts approved the current "Medical Evidence Protocol" developed by the Joint Committee in consultation with medical experts entitled *Revised Medical Evidence for Section 4.01(1) and Section 4.01(2) of Article 4 the Transfused HCV Plan and the Hemophiliac HCV Plan* which is annexed as **Exhibit "A"**. The Medical Evidence Protocol provides instruction to the Administrator in respect of evidence acceptable for the various disease level approvals, including for Disease Level 3.

12. Presently, option B of Disease Level 3 of the Medical Evidence Protocol provides that claimants may satisfy the medical evidence requirement at section 4.01(1)(c) of the Plans (triggering the payment of $30,000), if the class member delivers a satisfactorily completed form indicating the HCV Infected Person has undergone one of the following types of Compensable HCV Drug Therapy:

(i) interferon therapy;

(ii) combination interferon and ribavirin;

(iii) interferon combined with a drug other than ribavirin; or

(iv) ribavirin combined with a drug other than interferon.

13. Presently, option D of Disease Level 3 of the Medical Evidence Protocol provides that where options A to C have not been met, a class member can satisfy the medical evidence requirement in section 4.01(1)(c) of the Plans by:

(i) certification from a gastroenterologist, hematologist, infectious disease specialist or internist that:

a. the Approved HCV Infected Person has met or meets a protocol for Compensable HCV Drug Therapy consistent with the treatment decision factors set out in the most recent Canadian Association for the Study of the Liver (CASL) Consensus Guidelines for the Management of Hepatitis C, including some HCV disease indicator(s) in addition to a positive PCR test;

b. and which the certifying physician asserts is within generally accepted medical standards for recommending treatment.

14. Option D was added to the Medical Evidence Protocol in 2010 to cover the circumstance where options A to C in the Medical Evidence Protocol do not apply and a treating specialist

determines a class member appropriate for treatment based on a more subjective assessment of his or her condition in accordance with the factors delineated in the CASL Guidelines.

15. At the time option D was added to the Medical Evidence Protocol, the factors delineated in the CASL Guidelines related to interferon and ribavirin therapy, and so the option D alternate trigger for Disease Level 3 trigger was directly linked to Compensable HCV Drug Therapy as currently defined.

16. The CASL Consensus Guidelines in place from 2007 until May 2012 are annexed as **Exhibit "B"**

17. The Treating Physician Form completed by the physician to provide information to classify a person at the appropriate disease level, including Disease Level 3, provides a check list of options for the physician to complete that identify what drugs the patient is using for their treatment. Annexed as **"Exhibit C"** is a Treating Physician Form. The Medical Evidence Protocol and Treating Physician Form each reference the CASL Consensus Guidelines as one of the options to trigger the Disease Level 3 determination.

The Evolution of Treatment Utilizing DAAs

18. In 2011 Health Canada approved certain DAAs for use in treatment of HCV. Those drugs were prescribed with interferon or ribavirin. Since then, several DAAs have been approved for treatment with HCV. Some of the more recently approved DAAs are prescribed without interferon or ribavirin.

19. In 2012 and 2015 new CASL Guidelines were developed and published. The current CASL Guidelines (2015) are annexed as **Exhibit "D"**. The current CASL Guidelines include treatment regimens that are based on DAAs without interferon or ribavirin.

20. Compensable HCV Drug Therapy, as currently defined in the Plans, does not capture DAAs used for the treatment of HCV except in the circumstance where they are used in combination with interferon or ribavirin.

21. Class members who are receiving DAA treatment without interferon or ribavirin do not qualify for the $30,000 payment pursuant to section 4.01(1)(c) of the Plans (unless they meet

other criteria, i.e. option A or C which trigger Disease Level 3). In addition, these class members are not presently eligible for the $1000/month payment under section 4.05 of the Plans.

Adverse Side Effects of DAAs

22. The Joint Committee consulted with Dr. Vincent Bain and Dr. Bernard Willem on the issue of adverse side effects and DAAs. Dr. Bain's evidence (originally filed on the excess capital allocation motions) is included on these motions/applications. The Joint Committee's understanding following these consultations is that DAAs cause far fewer adverse side effects than treatment with interferon or ribavirin in terms of the number of patients who suffer side effects and in terms of the severity of the side effects experienced by those who do experience them, but some adverse side effects do occur.

23. During the class member consultation process prior to the June 2016 joint hearings of the courts on allocating excess capital, the Joint Committee received some information from class members during the townhall sessions and in the written submissions sent by class members that some have experienced side effects as a result of undergoing treatment with DAAs. The oral exchanges and written submissions do not allow the Joint Committee to be confident that all of these reports were made about treatment that excluded interferon and ribavirin, but it was clear that class members were experiencing fatigue and possibly other symptoms such as muscle soreness, and headaches while taking DAAs without interferon or ribavirin.

24. I am advised by the Administrator that, while they do not hear from many claimants complaining of side effects, those who do are saying they experienced headaches, nausea, fatigue and muscle/joint pain. Two class members have written letters to the Administrator regarding side effects while taking Harvoni including nausea, headaches, muscle pain and fatigue. One class member has submitted a request for review of the Administrator's decision to deny the claim for the $1,000 per month payment based on having experienced extreme fatigue, joint pain and headaches which interfered with her ability to care for her son and required her husband to take time off work. These assertions are supported by her treating physician.

25. The Joint Committee has also been advised by Ontario Fund Counsel and the Administrator that there is currently an appeal of the Administrator's refusal to approve the $1,000 per month payment in circumstances where the claimant claims to have suffered adverse side effects due to DAA treatment without interferon or ribavirin. The adverse side effects on

which the appeal is based are: the requirement to use birth control during the treatment and for six months after the treatment which delayed the plans of this class member and his wife to try to have children; weight gain; difficulty sleeping; fatigue; flu-like symptoms; and, increased sensitivity to exposure to sunlight.

26. The product monographs of the most commonly prescribed DAAs describe adverse reactions of DAAs observed in clinical trials.

27. Attached as **Exhibit "E"** is the product monograph for the DAA Harvoni. At page 10 it lists the adverse reactions to Harvoni observed in clinical trials, when taken without ribavirin. Included in the adverse reactions observed are:

(a) headache; and

(b) fatigue.

28. Attached as **Exhibit "F"** is the product monograph for the DAA Holkira PAK. At page 14 it lists the adverse reactions to Holkira Pak observed in clinical trials, when taken without ribavirin. Included in the adverse reactions observed are:

(a) fatigue;

(b) nausea;

(c) asthenia; and

(d) headache.

29. Attached as **Exhibit "G"** is the product monograph for the DAA Zepatier. At page 9 it lists the adverse reactions to Zepatier observed in clinical trials, when taken without ribavirin. Included in the adverse reactions observed are:

(a) fatigue;

(b) headache; and

(c) nausea.

30. Attached as **Exhibit "H"** is the product monograph for the DAA Epclusa approved for use by Health Canada on July 14, 2016. At page 9 it lists the adverse reactions to Epclusa observed in clinical trials, when taken without ribavirin. Included in the adverse reactions observed are:

(a) headache; and

(b) fatigue.

31. Attached as **Exhibit "I"** is the product monograph for the DAA Vosevi approved for use by Health Canada on August 16, 2017. At page 9 it lists the adverse reactions to Vosevi observed in clinical trials, when taken without ribavirin. Included in the adverse reactions observed are:

(a) headache;

(b) fatigue;

(c) diarrhea;

(d) insomnia; and

(e) asthenia.

32. Attached as **Exhibit "J"** is the product monograph for the DAA Maviret approved for use by Health Canada on January 25, 2017 and revised August 16, 2017. At page 8 it lists the adverse reactions to Maviret observed in clinical trials, when taken without ribavirin. Included in the adverse reactions observed are:

(a) headache;

(b) fatigue;

(c) nausea;

(d) diarrhea; and

(e) pruritis.

33. The adverse reactions set out above are those observed most frequently and/or in the greatest number of people during clinical trials. The monographs also include long lists of adverse reactions observed in a smaller number of persons during clinical trials and adverse reactions experienced during treatment.

34. The product monographs for Vosevi and Marivet contain a warning that cases of Hepatitis B virus reactivation have been reported in patients co-infected with Hepatitis C and Hepatitis B and treated with DAAs.

35. The Joint Committee is also aware that Health Canada has conducted a safety review of the DAA Galexos (simeprevir) in response to a Japanese publication that connected the use of

simeprevir with liver problems. As a result of this review, the manufacturer of Galexos (simeprevir) has updated prescribing information to warn about the risk of severe liver problems and related death. While the connection between simeprevir and this side effect is not certain, the Joint Committee is concerned that some of the potential side effects of DAAs may not yet be fully known or understood by the medical community. Attached to this affidavit as **Exhibit "K"** is a copy of the Health Canada Summary Safety Review - Galexos (Simeprevir) - Assessing the Potential Risk of Severe Liver Problems.

The Joint Committee's Recommendations

36. The Joint Committee recommends that the section of the Medical Evidence Protocol pertaining to Disease Level 3 be revised to add the following incidental wording to items iii and iv and to add item v, all of which are set out in bold below:

> **DISEASE LEVEL 3**
> To satisfy the medical evidence requirement at Section 4.01(1)(c) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator a satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has either:
>
> …
>
> (b) undergone one of the following types of Compensable HCV Drug Therapy:
>
> i. interferon therapy;
> ii. combination interferon and ribavirin therapy;
> iii. **treatment with** interferon combined with a drug other than ribavirin;
> iv. **treatment with** ribavirin combined with a drug other than interferon;
> **v. treatment with at least one direct-acting antiviral agent ("DAA") that has been approved by Health Canada in circumstances where the Treating Physician certifies that the HCV Infected Person suffered adverse side effects as a result of taking the DAA treatment; or**
>
> **…**

37. The Joint Committee also recommends that the section of the Medical Evidence Protocol pertaining to Disease Level 3 be revised by eliminating option D that is, the use of the CASL Guidelines as a protocol for treatment to satisfy the Disease Level 3 criteria of the Medical Evidence Protocol.

38. As discussed above, the current CASL Guidelines recommend some treatment regimens that do not include interferon or ribavirin and, as such, they no longer serve the purpose they were intended to serve as a proxy for meeting a protocol for treatment with Compensable HCV Drug Therapy as it is currently defined.

39. If the Courts accept the Joint Committee's proposal that DAA treatment qualify as Compensable HCV Drug Therapy in those circumstances where a treating physician certifies the class member has suffered adverse side effects as a result of taking the DAA treatment, the CASL Guidelines will still be too broad to serve as a protocol to assess progression to Disease Level 3 as they do not reflect the limited circumstances in which DAAs will be considered Compensable HCV Drug Therapy as proposed by the Joint Committee.

40. Moreover, the current CASL Guidelines recommend treatment for virtually all persons who are RNA positive. This would include persons who would be classified at Disease Level 1 or Disease Level 2 under the Plans and eliminate the current requirement included in option D under the Medical Evidence Protocol that persons experience "some HCV disease indicator(s) in addition to a positive PCR test", ie. some disease indicators that they have progressed beyond Disease Level 2. As such, the CASL Guidelines no longer serve the purpose they were intended to serve as identifying progression from one disease stage to a higher disease stage.

41. There are no adverse financial sufficiency implications in including DAAs as Compensable HCV Drug Therapy in the limited manner proposed as advancement to Disease Level 3 and the payment of the $1,000 per month are already considered in the restated liabilities ordered by the Courts in August 2016.

SWORN BEFORE ME at the City of Windsor in the County of Essex, this 13th day of October, 2017.

A Notary Public or Commissioner for taking Affidavits for Ontario

Shelley Lynn Woodrich, a Commissioner, etc., Province of Ontario, for Strosberg Sasso Sutts LLP, Barristers and Solicitors. Expires February 18, 2019.

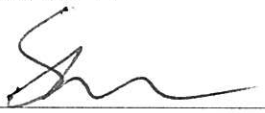
Heather Rumble Peterson

THE ATTACHED IS EXHIBIT "A" TO THE

AFFIDAVIT OF HEATHER RUMBLE PETERSON

SWORN BEFORE ME THIS 13TH DAY OF

OCTOBER, 2017



COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

REVISION: OCTOBER 2010

REVISED COURT APPROVED PROTOCOL FOR MEDICAL EVIDENCE FOR SECTION 4.01(1) AND 4.01(2) OF ARTICLE 4 OF THE TRANSFUSED HCV PLAN AND THE HEMOPHILIAC HCV PLAN

This Protocol sets out the acceptable medical evidence for Section 4.01(1) and 4.01(2) of Article 4 of the applicable Plan.

DISEASE LEVEL 1

To be entitled to the fixed payment provided for at Section 4.01(1)(a) of the applicable Plan, the Approved HCV Infected Person will have delivered to the Administrator the following:

(a) a satisfactorily completed TRAN2/HEMO2 Treating Physician Form; and

(b) a positive HCV Antibody Test in compliance with the SOP - Criteria for Acceptable HCV Antibody Test and PCR Test.

DISEASE LEVEL 2

To satisfy the medical evidence requirement at Section 4.01(1)(b) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator the following:

(a) a satisfactorily completed TRAN2/HEMO2 Treating Physician Form; and

(b) a positive PCR Test in compliance with the SOP -Criteria for Acceptable HCV Antibody Test and PCR Test.

DISEASE LEVEL 3

To satisfy the medical evidence requirement at Section 4.01(1)(c) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator a satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has either:

(a) developed fibrous tissue in the portal areas of the liver with fibrous bands extending out from the portal areas but without any bridging to other portal tracts or to central veins ("non-bridging fibrosis") as confirmed by a copy of a pathology report of a liver biopsy or by a positive result on Fibroscan (Elastography);

(b) undergone one of the following types of Compensable HCV Drug Therapy:

(i) interferon therapy;

(ii) combination interferon and ribavirin therapy;

(iii) interferon combined with a drug other than ribavirin;

(iv) ribavirin combined with a drug other than interferon; or

(c) met or meets the following protocol for Compensable HCV Drug Therapy:

(i) the HCV Infected Person is HCV RNA positive as confirmed by a copy of a PCR Test in compliance with the SOP-Criteria for Acceptance of HCV Antibody Test and PCR Test;

(ii) the HCV Infected person has medically demonstrated evidence of fibrotic changes to the liver as confirmed by a copy of a pathology report of a liver biopsy or by a positive result on Fibroscan (Elastography); or

(iii) the HCV Infected Person's ALTs were elevated 1.5 x normal for 3 months or more as confirmed by liver function test reports provided; and

(iv) the infection with HCV materially contributed to the elevated ALTs as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist.

(d) in circumstances where the above protocol is not met:

(i) certification by a gastroenterologist, hepatologist, infectious disease specialist or internist that:

A. the Approved HCV Infected Person has met or meets a protocol for Compensable HCV Drug Therapy consistent with the treatment decision factors set out in the most recent CASL Consensus Guidelines for the Management of Hepatitis C, including some HCV disease indicator(s) in addition to a positive PCR test;

B. and which the certifying physician asserts is within generally accepted medical standards for recommending treatment.

DISEASE LEVEL 4

To satisfy the medical evidence requirement at Section 4.01(2) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator a satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has developed fibrous tissue in the portal areas of the liver with fibrous bands bridging to other portal areas or to central veins but without nodular formation or nodular regeneration ("bridging fibrosis") as confirmed by a copy of a pathology report of a liver biopsy.

DISEASE LEVEL 5

To satisfy the medical evidence requirement at Section 4.01(1)(d) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator either:

(a) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person:

(i) has developed fibrous bands in the liver extending or bridging from portal area to portal area with the development of nodules and regeneration ("cirrhosis") as confirmed by:

A. a pathology report of a liver biopsy;

B. a Fibroscan report (Elastography);

C. an Ultrasound report;

D. an MRI report;

E. a CT Scan report; or

(b) in the absence of a liver biopsy, has been diagnosed with cirrhosis based on:

(i) three or more months with:

A. an increase in all gamma globulins with decreased albumin on serum electrophoresis as reported on a serum electrophoresis test provided;

B. a significantly decreased platelet count as reported on laboratory reports provided; and

C. an increased INR or prothrombin time as reported on laboratory reports provided;

none of which are attributable to any cause other than cirrhosis; and

(ii) a finding of hepato-splenomegaly, supported by a copy of an ultrasound report, an MRI report or a CT scan report of an enlarged liver and spleen, and one or more of the following peripheral manifestations of liver disease, none of which are attributable to any cause other than cirrhosis:

A. gynecomastia;

B. testicular atrophy;

C. spider angiomata;

D. protein malnutrition;

E. palm or nail changes characteristic of liver disease; or

(iii) one or more of the following, none of which are attributable to any cause other than cirrhosis:

A. portal hypertension evidenced by:

(1) an enlarged spleen which is inconsistent with portal vein thrombosis as confirmed by a copy of an ultrasound report; or

(2) abnormal abdominal and chest wall veins as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

B. esophageal varices as reported on an endoscopic report provided;

C. ascites as reported on an ultrasound report, an MRI report or a CT Scan report.

OR

(c) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with porphyria cutanea tarda:

(i) which failed to respond to one or more of the following treatments:

A. phlebotomy;

B. drug therapy - specifying the therapy;

C. Compensable HCV Drug Therapy; and

(ii) which is causing significant disfigurement and disability, a description of which is provided;

as confirmed by a 24 hour urine laboratory test report provided and a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the findings unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist.

OR

(d) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has thrombocytopenia unresponsive to therapy based on one or more of the following:

(i) a platelet count below 100 x 109 with:

A. purpura or other spontaneous bleeding; or

B. excessive bleeding following trauma;

as confirmed by a copy of a laboratory report and a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting either finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

(ii) a platelet count below 30 x 109, as reported on a laboratory report provided.

OR

(e) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with glomerulonephritis not requiring dialysis which is consistent with infection with HCV and copies of the following:

(i) a pathology report of a kidney biopsy which reports a finding of glomerulonephritis; and

(ii) a consultation or other report of a nephrologist confirming that the HCV Infected Person has glomerulonephritis not requiring dialysis which is consistent with infection with HCV unless the Treating Physician is a nephrologist.

DISEASE LEVEL 6

To satisfy the medical evidence requirement at Section 4.01(1)(e) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator either:

(a) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has had a liver transplant together as confirmed by a copy of an operative report of the transplant.

OR

(b) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has decompensation of the liver based on a finding of one or more of the following:

(i) hepatic encephalopathy as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

(ii) bleeding esophageal varices as confirmed by a copy of an endoscopic report;

(iii) ascites as confirmed by a copy of an ultrasound report, MRI report or CT Scan;

(iv) subacute bacterial peritonitis as confirmed by a copy of a laboratory report showing a neutrophil count of greater than 150 x 109 per ml in the ascitic fluid and/or positive ascitic culture;

(v) protein malnutrition as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

(vi) another condition a description of which is provided as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist.

OR

(c) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with hepatocellular cancer based on one or more of the following:

(i) a pathology report of a liver biopsy which reports hepatocellular cancer;

(ii) an alpha feto protein blood test report and a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

(iii) a report of a CT scan or MRI scan of the liver confirming hepatocellular cancer.

OR

(d) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with B-Cell lymphoma as confirmed by a copy of a consultation or other report of an oncologist or hematologist supporting the finding unless the Treating Physician is an oncologist or hematologist.

OR

(e) satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with symptomatic mixed cryoglobulinemia and copies of:

(i) the results of a blood test demonstrating elevated cryoglobulins; and

(ii) a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist.

OR

(f) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with glomerulonephritis requiring dialysis which is consistent with infection with HCV and copies of the following:

(i) a pathology report of a kidney biopsy which reports a finding of glomerulonephritis; and

(ii) a consultation or other report of a nephrologist confirming that the HCV Infected Person has glomerulonephritis requiring dialysis which is consistent with infection with HCV unless the Treating Physician is a nephrologist.

OR

(g) A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with renal failure and copies of:

(i) laboratory reports of serum creatinine and serum urea supporting the diagnosis; and

(ii) a consultation or other report of a nephrologist supporting the diagnosis unless the Treating Physician is a nephrologist.

Notes:

DISEASE LEVEL 3

1Note: The Administrator shall:

(a) accept the pathology report or Fibroscan report as evidence of non-bridging (or more severe) fibrosis if the pathology report or Fibroscan report is reported in terms which on their face are consistent with or exceed (in terms of severity of fibrosis) non-bridging fibrosis;

(b) accept the pathology report or Fibroscan Report as evidence of non-bridging (or more severe) fibrosis although the pathology report or Fibroscan report is not reported in such terms, if the Treating Physician is a pathologist, gastroenterologist, hepatologist, infectious disease specialist, or internist; or

(c) seek the assistance of a pathologist to interpret the pathology report. If necessary, the advising pathologist will request the pathology slides to make the determination.

DISEASE LEVEL 4

[2]Note: The Administrator shall:

(a) accept the pathology report as evidence of bridging (or more severe) fibrosis if the pathology report is reported in terms which on their face are consistent with or exceed (in terms of severity of fibrosis) bridging fibrosis;

(b) accept the pathology report as evidence of bridging fibrosis although the pathology report is not reported in such terms, if the Treating Physician is a pathologist, gastroenterologist, hepatologist, infectious disease specialist or internist; or

(c) seek the assistance of a pathologist to interpret the pathology report. If necessary, the advising pathologist will request the pathology slides to make the determination.

DISEASE LEVEL 5

[3]Note: The Administrator shall:

(a) accept the pathology report, Fibroscan report, CT Scan report, Ultrasound report or MRI report as evidence of cirrhosis if the applicable report is reported in terms which on their face are consistent with or exceed (in terms of severity of fibrosis) cirrhosis;

(b) accept the pathology report, Fibroscan report, CT Scan report, Ultrasound or MRI report as evidence of cirrhosis although the pathology report is not reported in such terms, if the Treating Physician is a pathologist, gastroenterologist, hepatologist, infectious disease specialist or internist; or

(c) seek the assistance of a pathologist to interpret the pathology report. If necessary, the advising pathologist will request the pathology slides to make the determination.

DISEASE LEVEL 6

[4]Note: In the event that the Treating Physician specifies another condition at 2f), the Administrator shall seek the advice of a gastroenterologist, hepatologist, infectious disease specialist or internist as to whether the diagnosis of decompensation of the liver would be generally accepted by the medical community in those circumstances.

THE ATTACHED IS EXHIBIT "B" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 13TH DAY OF OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP.
Barristers and Solicitors.
Expires February 18, 2019.

Management of chronic hepatitis C: Consensus guidelines

Morris Sherman MD PhD[1], Stephen Shafran MD[2], Kelly Burak MD[3], Karen Doucette MD[2], Winnie Wong MD[2], Nigel Girgrah MD[1], Eric Yoshida MD[4], Eberhard Renner MD[5], Philip Wong MD[6], Marc Deschênes MD[6]

M Sherman, S Shafran, K Burak, et al. Management of chronic hepatitis C: Consensus guidelines. Can J Gastroenterol 2007;21(Suppl C):25C-34C.

Since the last consensus conference on the management of chronic viral hepatitis, a number of studies looking at modifications of the standard course of treatment have been published. These changes have been sufficiently substantive to warrant review to determine whether any changes in the recommended treatment algorithms are needed. A consensus development conference was held in January 2007, and the present document highlights the results of the presentations and discussion about these issues. It reviews the epidemiology of hepatitis C in Canada, treatment of acute hepatitis C and new algorithms in chronic hepatitis C, including retreatment of previous treatment failures. In addition, sections on management of hepatitis C in special populations have been updated. There is also a section on the use of hematopoietic growth factors to help manage patients on therapy. The document should be read in conjunction with the previous document to identify changes. Some recommendations made in the previous document remain and are not discussed here.

Key Words: *Acute hepatitis C; Chronic hepatitis C; Epidemiology; Erythropoietin*

La prise en charge de l'hépatite C chronique : Des lignes directrices consensuelles

Depuis la dernière conférence consensuelle sur la prise en charge de l'hépatite virale chronique, plusieurs études ont été publiées sur les modifications de l'évolution standard du traitement. Ces changements ont été assez importants pour justifier un examen afin de déterminer s'il faut modifier les algorithmes de traitement recommandés. Une conférence d'élaboration de lignes directrices consensuelles a eu lieu en janvier 2007, et le présent document expose les résultats des présentations et des discussions sur le sujet. Il traite de l'épidémiologie de l'hépatite C au Canada, du traitement de l'hépatite C aiguë et des nouveaux algorithmes de l'hépatite C chronique, y compris une reprise du traitement après des échecs thérapeutiques. De plus, on a mis à jour les parties sur la prise en charge de l'hépatite C dans les populations spéciales. Une autre partie porte sur le recours aux facteurs de croissance hématopoïétiques pour contribuer à prendre en charge les patients en cours de traitement. Il faut lire le présent document conjointement avec le document précédent afin de déterminer les changements apportés. Certaines recommandations énoncées dans le document précédent demeurent valables et ne sont pas abordées dans celui-ci.

EPIDEMIOLOGY OF HEPATITIS C IN CANADA

Chronic hepatitis C continues to be a significant medical and economic burden to Canadians. It is associated with an excess mortality that will continue to increase for many years into the future (Figure 1). Infected individuals may have a diminished quality of life.

There are no large-scale representative studies to determine the prevalence of chronic hepatitis C in Canada. However, sophisticated modelling techniques suggest that the prevalence is approximately 0.8% to 1% and increasing over time (1). The annual estimated hepatitis C-related mortality and the rate of cure on therapy is exceeded by the number of new infections and the number of infected persons immigrating to Canada, so that the prevalence of hepatitis C virus (HCV) infection is increasing and will continue to increase for the foreseeable future (Table 1). Currently, approximately 65% of the estimated cases in Canada have been identified. Predictions are that by 2022, the number of hepatitis C-related deaths will increase by one-third (Figure 1) (1).

Approximately 20% of hepatitis C in Canada occurs in the immigrant community, where access to health care may be less than optimal (1). Countries with high prevalence rates for hepatitis C, and that provide Canada with immigrants, include Egypt, Somalia, Pakistan, Bangladesh and Vietnam. In addition, immigrants from southern Europe (mainly Italy, Greece and Spain) who came to Canada years ago have a high prevalence of hepatitis C, often due to silent epidemics in their home countries between the end of World War II and approximately 1975. HCV infection from transfusion of blood products accounts for only approximately 13% of all cases. Injection drug use (IDU), current or past, accounts for more than 56% of all HCV infections in Canada (Table 2).

Almost all new HCV infections acquired in Canada are related to IDU through sharing of injection equipment. However, immigration now contributes approximately 33% of all new cases of hepatitis C (1).

Given the alarming estimates of future disease burden, more accurate information about the incidence and prevalence of hepatitis C and its complications are urgently needed to inform health care planning and resource allocation.

Recommendation 1: A large-scale, population-based seroprevalence survey should be mounted to accurately assess the prevalence of hepatitis C in Canada. The design of the study should take into account the known risk factors and specifically sample populations with known high endemicity (III [see Table 3 for levels of evidence]).

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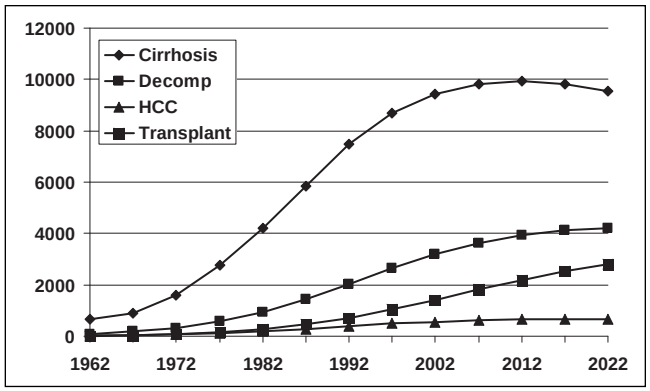

Figure 1) *Modelled prevalence of hepatitis C virus sequelae in Canada, 1962 to 2022. Reproduced from reference 1. Decomp Decompensated liver disease; HCC Hepatocellular carcinoma*

TABLE 1
Estimated hepatitis C virus (HCV) prevalence in Canada, July 1998 to December 2002

HCV prevalence, July 1998	240,000
Annual new infections	6600
HCV immigration	2000
Annual mortality	4700
HCV prevalence, December 2002	253,300

Recommendation 2: The current surveillance and data collection and reporting process needs to be expanded to better capture the incidence of new cases (III).

Recommendation 3: Steps must be taken to reduce the incidence of HCV infection among injection drug users and users of crack cocaine. These may include expansion of safe injection sites and needle exchange programs, and provision of single-use injection or crack-smoking equipment. Legal impediments to such programs must be removed. This is not a crime issue; this is a public health issue because injection drug users are increasingly becoming the reservoir for new infections (III).

Recommendation 4: Programs should be established to identify the approximately 35% of HCV-infected individuals who are unaware of their infection because there is curative therapy. For those for whom cure is not possible, lifestyle modifications to reduce the rate of disease progression can be advised (III).

ACUTE HEPATITIS C

Most cases of acute hepatitis C are asymptomatic and seldom diagnosed. Nonetheless, acute hepatitis C represents an opportunity to offer effective therapy. Acute hepatitis C is usually diagnosed under three circumstances: documented seroconversion, known exposure (eg, needle-stick exposure) and acute, clinical hepatitis.

There has been a high rate of spontaneous clearance of virus following acute hepatitis C, which was more than 50% in some studies (2). The younger the age of the infection, the more likely is spontaneous clearance of the virus. Icteric hepatitis predicts spontaneous clearance with a high accuracy. Clearance usually occurs within 14 weeks of exposure. Most patients clear virus within 12 weeks. However, a single negative HCV RNA is insufficient to confirm clearance, and the test should be repeated at least once.

TABLE 2
Hepatitis C virus (HCV) prevalence by exposure category in Canada, 2002

	Population	HCV prevalence rate, %	HCV prevalence	Proportion, %
IDU	91,000	55	49,900	20
Previous IDU	181,400	49	89,400	36
IDU, total	272,500		139,300	56
Transfusion	2,748,200	1.2	32,900	13
Hemophilia		57	1200	0.5
Other	28,023,900	0.26	73,800	30
Total	31,046,600	0.80	247,200	100

IDU Injection drug use

TABLE 3
Levels of evidence according to study design

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-controlled studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinion of respected authorities; descriptive epidemiology

Data from reference 97

Because seroconversion is unpredictable, treatment should be considered in all patients. Treatment is most effective when started before 12 weeks (3,4). Sustained virological response (SVR) rates of greater than 90% have been described using pegylated interferon (PEG IFN) monotherapy (5-7).

Recommendation 5: Patients with acute, icteric hepatitis C can be observed for up to 12 weeks to determine whether spontaneous clearance occurs. If clearance has not occurred, treatment should be initiated by 12 weeks (II-2).

Recommendation 6: In patients with acute, nonicteric hepatitis C, the likelihood of spontaneous clearance is lower, so treatment should start soon after diagnosis (II-2).

Recommendation 7: Treatment is with PEG IFN-alpha monotherapy. Genotypes 2 and 3 should be treated for 12 weeks, and genotype 1 should be treated for 24 weeks (I).

CHRONIC HEPATITIS C

Testing for hepatitis C should be undertaken in patients with abnormal aminotransferases and/or risk factors for contracting hepatitis C. These risk factors include past or active IDU, blood transfusion before the introduction of second-generation anti-HCV assays in 1991, and immigration from countries of high prevalence where medical procedures may have been dispensed using improperly sterilized needles or unscreened blood products (8,9).

The initial test should be an antibody test against HCV (third-generation enzyme-linked immunoassay). A sensitive HCV RNA assay may be used for confirmation.

Recommendation 8: All patients with chronic hepatitis C should be assessed to determine whether they may benefit from therapy (III).

Whether treatment is offered should be decided by weighing the risks and the benefits for a particular patient. This decision

is complex and should consider risk of disease progression to end stage, probability of a favourable response to therapy, risk of adverse effects with therapy and comorbid conditions. The patient's wishes must also be taken into consideration. Although patients with advanced liver disease are most in need of therapy, those with early disease are most likely to clear the virus.

The assessment for suitability for therapy should include a review of the patient's history for past or current psychiatric disease, seizures, cardiac or renal disease, autoimmune disease, and alcohol or drug addiction.

Further laboratory testing includes HCV genotyping and viral load, thyroid-stimulating hormone, antinuclear antibody, serum or urine beta-human chorionic gonadotropin (for women of reproductive age), and an electrocardiogram (if the patient is older than 50 years or has a history of heart disease). A fundoscopic examination to rule out retinopathy in patients over 50 years of age or who have high blood pressure or diabetes mellitus is advisable. Although IFN can induce a retinopathy, there are no data to suggest that the risk is higher or that retinopathy is more severe in patients with pre-existing retinopathy. The retinopathy resolves on withdrawal of IFN.

Liver biopsy is the most sensitive measure of severity of liver damage. Although not mandatory, it is recommended before the initiation of therapy. In patients who elect not to be treated, a biopsy showing mild disease is helpful to support that decision.

Recommendation 9: Sensitive qualitative HCV RNA testing, HCV viral load testing and genotype testing are essential to the management of patients with chronic hepatitis C. Results should be reported in IU/mL and be available in a timely manner (III).

Because of the theoretical risk of teratogenicity associated with ribavirin, male and female patients must use effective contraception while on therapy and for six months after completion of therapy. However, no associated fetal abnormalities have been described in pregnancies where either parent was taking ribavirin at the time of conception or in early pregnancy.

Despite more effective and tailored therapy, it appears that less than one-third of patients in large hepatitis C clinics have been treated (10). The most common reasons for ineligibility other than patient refusal include a high likelihood of noncompliance, low blood counts, advanced age, psychiatric conditions, substance abuse, coronary disease, cerebrovascular disease, retinopathy, uncontrolled diabetes, autoimmune disorders and serious pulmonary disease.

CONTRAINDICATIONS

There are very few absolute contraindications to treatment (Table 4). There are anecdotal reports of successful therapy in patients who might have been excluded from therapy for most of the previously defined contraindications. Therefore, most contraindications are considered to be relative rather than absolute. In most cases, treatment of these patients requires a high degree of expertise, and therefore patients with relative contraindications should be treated in expert centres. A history of substance abuse is not a contraindication to therapy. Stable patients on a methadone maintenance program can be treated successfully (11). Patients who do not achieve complete abstinence from alcohol can also be treated successfully (12). Recent alcohol use reduces the likelihood of completing treatment, but for those who complete treatment, the response is similar to nondrinkers. Patients with prior alcohol or other substance abuse should undergo a period of abstinence before initiating therapy to allow the abstinence to become more stable. In most cases, this should be at least six months, although this can be individualized.

TABLE 4
Contraindications for treatment with pegylated interferon and ribavirin

Conditions that are no longer contraindications	Normal alanine aminotransferase
	Stable methadone maintenance
	Neutropenia, anemia or thrombocytopenia
	Controlled seizure disorder
	Older than 65 years
	Alcohol use
Relative contraindications	Major depression
	Major psychosis
	Autoimmune disease
	Injection drug use
	Renal failure (including dialysis)
Strong but not absolute contraindications	Alcohol abuse
	Hepatic decompensation
	Coronary artery disease
	Solid organ transplantation (except liver)
Absolute contraindications	Pregnancy

Low blood counts can often be corrected before therapy. Patients with normal alanine aminotransferase (ALT) should be considered for treatment; some will have significant histological liver disease. They respond to therapy in the same manner as do those with elevated ALT (13). Older patients can be treated successfully (14).

Generally, in patients with substance abuse, alcoholism and psychiatric conditions, the prime factor determining whether treatment is feasible is the likelihood of poor adherence. Patients who are likely to be nonadherent for any reason are generally not good candidates for treatment. However, adherence can be greatly enhanced when therapy is provided in a supervised, multidisciplinary setting.

Patients with a history of depression are not necessarily at a higher risk for depression on therapy. However, patients who are depressed at the start of therapy are at higher risk for worsening of symptoms. Onset of depression during therapy is not a reason to discontinue treatment because there are many antidepressants that can be used to successfully treat these symptoms. However, suicidal ideation or the development of mania are treatment-related medical emergencies and must lead to complete withdrawal of therapy.

Some conditions, such as severe cardiac disease or other causes of reduced life expectancy due to comorbid disease, or organ transplants (other than liver transplant), still represent contraindications to therapy, but generally many of the contraindications are modifiable or treatable; thus, a patient currently deemed ineligible for therapy should be re-evaluated at a later date.

THERAPY FOR HCV

The best results have been obtained with combination PEG IFN and ribavirin (15,16). There are two formulations of PEG IFN available, PEG IFN-alpha-2a and PEG IFN-alpha-2b. They differ by virtue of the size and configuration of the polyethylene glycol molecules bound to the IFN molecule. The two formulations of PEG IFNs have not been compared head to head but appear to be equivalent choices for therapy.

TABLE 5
Definition of treatment responses

Rapid virological response	HCV RNA negative (less than 50 IU/mL) at week 4
Early virological response	≥ 2 log decline in HCV RNA at week 12 (EVC plus PVR) or HCV RNA negative at 12 weeks
Aviremic or EVC	HCV RNA negative (less than 50 IU/mL) at week 12
Viremic response or PVR	≥ 2 log decline in HCV RNA at week 12, but HCV RNA still positive
Sustained virological response	HCV RNA negative 24 weeks after end of treatment

EVC Early virological clearance; HCV Hepatitis C virus; PVR Partial virological response

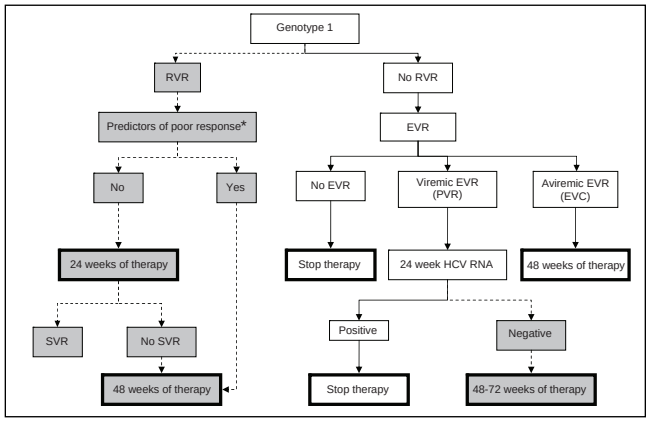

Figure 2) *Algorithm for the management of patients with hepatitis C virus (HCV) genotype 1 infection on therapy with pegylated interferon and ribavirin. The dotted arrows and shaded boxes represent new treatment algorithms based on viral kinetics. The solid arrows and clear boxes represent the standard algorithms. *Advanced fibrosis, high viral load, high body mass index, older age, African American race, HIV coinfection or immunosuppression. EVC Early virological clearance; EVR Early virological response; PVR Partial virological response; RVR Rapid virological response; SVR Sustained virological response*

The definitions of response at different time periods during therapy are given in Table 5.

RIBAVIRIN DOSE

PEG IFN and ribavirin remains the mainstay of hepatitis C therapy. It is clear that optimizing the ribavirin exposure, particularly during the first 12 weeks of therapy, is critical for achieving a good response to therapy (17,18).

Unfortunately, in Canada, ribavirin is bundled with IFN, reducing the discretion of the physician to give additional ribavirin if considered necessary. Ribavirin is dosed by weight. However, in genotype 1 infection, it is not certain whether patients weighing less than 74 kg will achieve the optimal results using 800 mg of ribavirin, nor whether patients heavier than 88 kg will have better outcomes on 1400 mg of ribavirin than on 1200 mg. It is also not certain whether heavier patients with genotype 2 infection need more than 800 mg of ribavirin.

STANDARD TREATMENT OF HEPATITIS C

Standard and modified treatment algorithms are shown in Figures 2 and 3.

Recommendation 10: Genotypes 1, 4, 5 and 6 should be treated with either of the following:

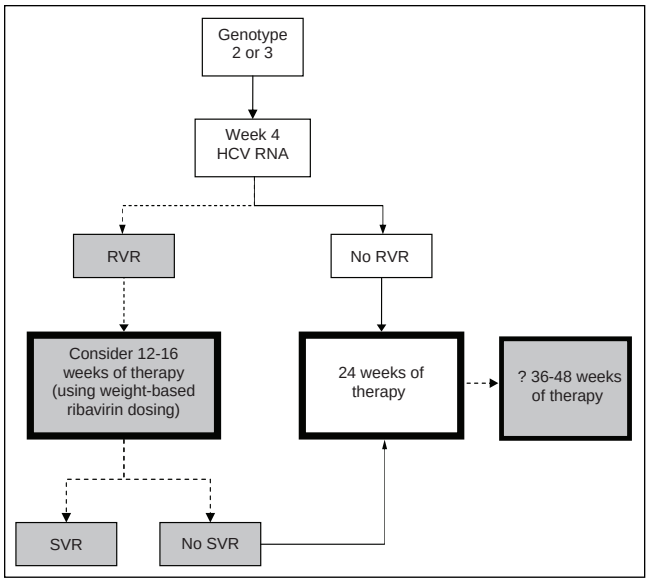

Figure 3) *Algorithm for the management of patients with hepatitis C virus (HCV), genotype 2 or 3, on therapy with pegylated interferon and ribavirin. The dotted arrows and shaded boxes represent new treatment algorithms based on viral kinetics. The solid arrows and clear boxes represent the standard algorithms. ? Consider 36 to 48 weeks of therapy, but the evidence is weak. RVR Rapid virological response; SVR Sustained virological response*

a) PEG IFN-alpha-2a (Pegasys RBV, Hoffmann-La Roche Ltd, Canada) 180 µg subcutaneously once weekly and ribavirin 1000 mg to 1200 mg daily given orally in two divided doses. The dose of ribavirin given depends on whether the patient weighs more or less than 75 kg (I).

b) PEG IFN-alpha-2b (Pegetron, Schering-Plough Canada Inc) 1.5 µg/kg subcutaneously once weekly and ribavirin 800 mg to 1200 mg daily given orally in two divided doses. The dose of ribavirin depends on the patient's weight, targeting a daily dose of ribavirin greater than 13.5 mg/kg, and is given orally in two divided doses (I).

Recommendation 11: Therapy is given for 48 weeks for genotypes 1, 4, 5 and 6. In patients who do not achieve an early virological response (EVR) or are still viremic after 24 weeks, therapy should be discontinued because the likelihood of SVR is negligible (I).

Recommendation 12: Genotype 2 or 3 infection should be treated with either of the following:

a) PEG IFN-alpha-2a 180 µg subcutaneously once weekly and ribavirin 800 mg daily given orally in two divided doses. There are data from randomized controlled studies and from other sources showing that for genotype 2 or 3 infection, 800 mg/day of ribavirin is sufficient (I).

b) PEG IFN-alpha-2b 1.5 µg/kg subcutaneously once weekly with ribavirin. The manufacturers suggest that ribavirin be dosed by weight in this group as well, but the evidence that more than 800 mg/day is required is not convincing (I).

Recommendation 13: The standard duration of therapy for patients with genotype 2 or 3 infection is 24 weeks (I).

SVR rates for genotype 1 infection range from 42% to 46% (15,16,18). SVR rates of 72% to 80% have been achieved for treatment of genotype 2 and 3 infections (15,16,18). Although infections with genotypes other than 1, 2 and 3 are less common and results of treatment are less well defined, the results appear to be better than those for genotype 1 but not as good as those for genotypes 2 and 3.

NEW REGIMENS FOR TREATMENT OF HEPATITIS C

There is increasing evidence that the standard duration of therapy is not optimal for many patients with chronic HCV infection. Modifying the duration of therapy based on viral kinetics can maximize SVR rates while limiting the toxicities and costs associated with treatment. An essential component in the decision to shorten therapy is an assessment of rapid virological response (RVR) (Table 5).

Recommendation 14: Week 4 HCV RNA testing must be available in a timely manner to all clinicians treating chronic hepatitis C (III).

Genotype 1

In those who achieve RVR who have no predictors of poor response (advanced fibrosis, high viral load, high body mass index, older age, African American race, HIV coinfection or immunosuppression), therapy may be shortened to 24 weeks. In this subgroup, SVR rates of 88% to 89% can be achieved (19-21).

Recommendation 15: Patients with genotype 1 infection and no predictors of poor response who achieve an RVR may be treated to 24 weeks (II-3). Before terminating treatment at 24 weeks, the patient should be aware that if relapse occurs, retreatment for 48 weeks will be necessary. Early withdrawal of therapy should not be undertaken unless funding is available for a second, more standard course of therapy (III).

Some patients may achieve a 2 log drop in HCV RNA by week 12 but do not achieve undetectable HCV RNA. This is defined as partial virological response (PVR) or viremic EVR. These patients may then clear HCV RNA by week 24. Such patients have been termed 'slow responders'. A preliminary study (22) suggested that prolonging therapy to 72 weeks may be of benefit in this subgroup. Subsequently, several studies (23-26) comparing 48 to 72 weeks of therapy in genotype 1 patients suggested a benefit of prolonged therapy in slow responders. Some published studies (27), however, used 800 mg of ribavirin, and the benefit of prolonged therapy with weight-based ribavirin dosing remains uncertain.

Recommendation 16: Prolonged therapy to 72 weeks may be considered in genotype 1 patients with PVR who are HCV RNA-negative at week 24 (I). Funding for prolonged treatment should be supported by provincial drug formularies under appropriate circumstances (III).

Genotypes 2 and 3

In patients who have an RVR, 12 to 16 weeks of therapy results in SVR in 80% to 100% of genotype 2 patients and in 77% to 85% of genotype 3 patients (27-32). However, in a large, randomized trial (32), 24 weeks of therapy was superior to 16 weeks in those with RVR in both genotype 2 (91% versus 80%) and genotype 3 (89% versus 84%) subgroups. However, this study used 800 mg of ribavirin, and although the optimal dose of ribavirin has not been adequately defined, higher doses of ribavirin may be required in shortened regimens (33).

Recommendation 17: Patients with genotype 2 or 3 infection who achieve RVR may have therapy withdrawn at 12 or 16 weeks if they have been receiving weight-based ribavirin dosing (I). Before terminating treatment early, the patient should be aware that if relapse occurs, retreatment for 24 weeks will be necessary. Early withdrawal of therapy should not be undertaken unless funding is available for a second, more standard course of therapy (III).

RVR is the best predictor of SVR. In those who fail to achieve RVR, SVR rates with 24 weeks of therapy are disappointing, particularly in patients with genotype 3 infection (41% to 58%), but also in patients with genotype 2 infection (50% to 89%) (27-32). It is possible that prolonging therapy may produce a higher SVR; however, to date, no study of prolonged therapy in this population has been carried out. Further data are needed to establish the role of prolonged therapy (greater than 24 weeks) in patients with genotype 2 or 3 infection who fail to achieve an RVR. There was no consensus as to whether prolonged treatment should be offered to this group of patients.

Treatment algorithms for genotypes 1, 2 and 3 incorporating treatment decisions based on RVR are shown in Figures 2 and 3.

Genotype 4

The standard duration of therapy in patients with genotype 4 infection is 48 weeks. This results in an SVR of 40% to 79% (34-36). The week 12 HCV RNA can be used to predict response; as in genotype 1 infection, the lack of an EVR has a high negative predictive value and treatment should be discontinued. In patients with fibrosis scores of 0 to 2 on liver biopsy and a viral load at baseline less than 800,000 IU/mL, treatment duration can be shortened to 36 weeks (36).

Maintenance therapy

In addition to its antiviral action, IFN has many other properties, including antiproliferative and antiangiogenic activity, that may reduce the rate of complications in patients with advanced fibrosis who fail to achieve an SVR. Three large trials are ongoing to evaluate the role of long-term, low-dose (maintenance) therapy in this population. At the present time, there is insufficient evidence to recommend maintenance therapy in nonresponders.

RETREATMENT OF PREVIOUS TREATMENT FAILURES

Compared with the currently available PEG IFN and ribavirin combination products, the previous antiviral therapies of standard IFN monotherapy and standard IFN and ribavirin combination therapy were associated with more treatment failures. The exact number of previous treatment failures in the community is unknown, but given the number of patients treated before the licensure of the PEG IFN and ribavirin products, it is likely that the pool of standard IFN treatment failures is not inconsequential. Although the limited intrinsic potencies of the previous antiviral therapies contributed substantially to treatment failure, other secular factors, including suboptimal dosing in response to monitoring laboratory blood work or adverse clinical effects, nonadherence because of lack of nursing support, inadequate patient education and physician inexperience, may

have contributed. It must also be appreciated that the contemporary recommendations for dose reduction and drug withdrawal are not as restrictive or cautious as in previous years given the additional years of experience with HCV IFN-based therapies in general. Thus, among patients who failed previous therapy, there is likely to be a significant proportion who failed because of early withdrawal, overly aggressive dose reductions or missed doses rather than because of true nonresponse or relapse.

There are presently seven studies (37-43) that evaluated retreatment of both relapsers and nonresponders, and another large study (44) has been reported in abstract form. Of these studies, two (37,43) were randomized clinical trials that compared two doses of PEG IFN-alpha-2b plus ribavirin, and the other studies were single-arm observational studies that administered PEG IFN-alpha-2b plus ribavirin or PEG IFN-alpha-2a plus ribavirin.

In general, relapsers to previous IFN-based therapy had a superior response to PEG IFN and ribavirin combination therapy (34% to 55%) than nonresponders to previous therapy (8% to 26%). Genotype 1 relapsers responded less well to PEG IFN and ribavirin combination therapy (34% to 53%) than nongenotype 1 patients (ie, mostly genotypes 2 and 3) (42% to 70%). Among nonresponders to previous standard IFN therapy, the SVR of genotype 1 patients ranged from 5% to 22%, whereas that of nongenotype 1 nonresponders ranged from 19% to 57%. The maximum response reported for genotype 1 nonresponders to previous combination therapy was 19% to 20%. Most studies reported that the response was inversely proportional to the fibrosis score. The largest study (44), with 1046 patients, reported that among genotype 1 nonresponders to previous IFN-based therapy, the SVR ranged from 23% for those with bridging fibrosis and a platelet count greater than 125×10^9/L to 9% for those with cirrhosis and a platelet count of less than 125×10^9/L. Failure to achieve EVR at week 12 of therapy has also been reported to be 100% predictive of failure to achieve SVR in genotype 1 patients. In the two studies (37,38) that randomized PEG IFN-alpha-2b plus ribavirin based on weight-based dosing (ie, 1.0 μg/kg versus 1.5 μg/kg of PEG IFN), a nonstatistically significant trend was reported in favour of the higher weight-based dose.

Consensus IFN has also been shown to improve the response rates in previous treatment failures, including previous failures on PEG IFN and ribavirin (45). The treatment regimens used require daily doses of IFN, and ribavirin was not part of the regimen. What role consensus IFN should play in retreating patients is not clear.

Recommendation 18: Patients who relapsed to previous standard IFN-based therapies respond well to PEG IFN and ribavirin combination therapy, regardless of genotype, and should be offered therapy (II-2).

Recommendation 19: Given the uncertainty of the treatment dose of IFN and the duration of standard IFN monotherapy, as well as its general inferiority to combination regimens with ribavirin, patients who were previous treatment failures with standard IFN monotherapy should be offered treatment with PEG IFN and ribavirin combination therapy regardless of whether the treatment failure was due to nonresponse or relapse and regardless of genotype (II-2).

Recommendation 20: Patients who were nonresponders to previous standard IFN and ribavirin combination therapy may be considered for treatment with PEG IFN and ribavirin combination therapy. If treatment is offered, a quantitative HCV RNA determination at baseline and at week 12 of therapy should be performed. Failure to achieve EVR should lead to treatment withdrawal (I).

MONITORING WHILE ON THERAPY

Therapy with PEG IFN and ribavirin is associated with numerous possible side effects. Some adverse events can be severe, even life-threatening and irreversible. Therefore, close patient monitoring by the treatment team is imperative. Laboratory monitoring during therapy involves the following: complete blood count at weeks 1, 2, 4, 6 and 8, and monthly thereafter; aspartate aminotransferase; ALT; alkaline phosphatase; bilirubin; international normalized ratio; albumin; glucose; creatinine; urinanalysis; thyroid-stimulating hormone every three months; and pregnancy testing periodically (46). RVR is assessed by qualitative HCV RNA testing at week 4. EVR is assessed by quantitative HCV RNA testing at week 12 in those with genotype 1 infection. Failure to achieve EVR should lead to treatment withdrawal. In those who achieve an EVR but do not achieve undetectable viral load, a qualitative HCV RNA test should be performed at week 24, and a positive test should result in treatment withdrawal.

MANAGEMENT OF HEPATITIS C IN SPECIAL CIRCUMSTANCES

Renal failure

HCV infection is more frequent in dialysis patients than in the general population (47,48). Anti-HCV may not be positive, even in the presence of HCV RNA. ALT elevation often does not reflect disease severity in this population. Liver biopsy may be necessary to establish disease severity, despite the potential additional bleeding risk. Transjugular biopsy can also be considered. HCV infection adversely affects patient and graft survival after kidney transplantation. However, this is not a contraindication to transplantation. Overall outcomes in HCV-infected individuals remain within an acceptable range, with poor outcomes generally seen in those with advanced fibrosis at transplantation. IFN-based therapy before transplantation improves post-transplant outcomes (48,49). IFN-based therapy increases the risk of rejection and is generally contraindicated after solid organ transplantation (except for liver transplantation).

PEG IFN-alpha 2b and ribavirin are excreted by the kidneys. Ribavirin is not dialyzable. Therefore, both PEG IFN-alpha-2b and ribavirin carry the risk of accumulating, resulting in an increased risk of toxicity, in patients with renal failure, particularly in those on dialysis. However, both PEG IFN-alpha-2a and PEG IFN-alpha-2b have recently been used in small series (50-52) of HCV-infected hemodialysis patients, in combination with very low dose ribavirin. The ribavirin dose was controlled by ribavirin blood level monitoring. Despite reported SVR rates of 20% to 70% and an acceptable tolerability (except for an increase in erythropoietin requirements), the database is too small to allow general recommendations. At this point, patients with advanced renal failure should only be treated with PEG IFN and ribavirin in specialized centres that are able to perform ribavirin blood level monitoring. In patients with end-stage renal disease, hepatitis C treatment should generally be reserved for those who are candidates for renal transplantation. IFN is poorly tolerated in this population and response rates to treatment are low. Competing risks for mortality in this population also reduce the likelihood of benefit from hepatitis C treatment.

Recommendation 21: Treatment of hepatitis C in renal failure is best undertaken in conjunction with a nephrologist, and should be reserved for experts (III).

Decompensated liver disease

PEG IFN and ribavirin have limited efficacy and a poor safety and tolerability profile in patients with decompensated liver disease (53-55). Anti-HCV treatment in these patients should never delay referral for transplant evaluation, and should only be carried out at a liver transplantation or other expert centre.

Recommendation 22: Treatment of patients with decompensated liver disease should be conducted in conjunction with a liver transplant team and by physicians familiar with the management of these diseases (III).

Solid organ transplantation

IFN is usually contraindicated after solid organ transplantation because of the risk of exacerbating rejection. Loss of kidney grafts has been reported after IFN use. In patients with life-sustaining organ transplants (eg, heart or lung), IFN should be avoided given the risk of rejection and graft loss. In renal transplant recipients, IFN-based therapy may be considered in those with progressive HCV-related liver disease or HCV-induced renal disease if the benefits are thought to outweigh the risks (rejection, graft loss and return to dialysis) and after discussion with the patient.

However, IFN can be used post-liver transplantation for treatment of hepatitis C. Rejection may occur in this setting but is generally easily treated if detected early.

Treatment of hepatitis C in transplant recipients should only be conducted in expert centres.

Cryoglobulinemia

Mixed type II cryoglobulinemia is present in up to 50% of patients with HCV infection and may lead to symptomatic vasculitis in a minority of patients. SVR rates of 44% to 78% have been achieved with PEG IFN and ribavirin in small series of patients (56-58). SVR was associated with clinical improvement of the vasculitis in the majority of, but not all, patients (59). Patients with symptomatic type II cryoglobulinemia vasculitis may benefit from antiviral combination therapy, even if viral eradication is not achieved. The optimal therapeutic scheme remains to be defined. There is insufficient information to make any specific recommendations.

Chronic anemia

Antiviral therapy with standard dose PEG IFN-alpha and ribavirin in HCV-infected patients with thalassemia major has been shown to be effective but increases transfusion requirements (60). As in other patients, comorbidities and the likelihood of their HCV-related liver disease ever reaching relevant morbidity and mortality during their life expectancy has to be taken into account when deciding on therapy in these patients. Similar considerations apply to patients with other forms of chronic anemia. These patients may need to be supported by transfusion during therapy rather than by the use of erythropoietin.

Recommendation 23: Patients with chronic anemia can be treated with IFN and ribavirin. This requires collaboration between the hematologist and the physician treating the hepatitis C (II-2).

Lymphoma

HCV infection can be associated with some forms of non-Hodgkin lymphoma although a causal relationship has not consistently been documented (61-63). In small, uncontrolled series (64,65), IFN-based anti-HCV therapy was reported to lead to a complete hematological response in greater than 50% of patients when associated with HCV suppression. The optimal drug dosage and duration of therapy remain to be defined. There is insufficient information to make any specific recommendations.

HCV infection in hemophiliacs

Hemophilia is not a contraindication for antiviral therapy with the current regimens of PEG IFN and ribavirin. With the exception of liver biopsy, the same criteria for indication and conduct of therapy apply as for HCV-infected patients without hemophilia. Liver biopsy is unpopular in the hemophilia population but can be safely performed by the transjugular route with appropriate clotting factor support.

HCV-HIV coinfection

Approximately 20% of HIV-infected patients are coinfected with HCV (66). HCV-related end-stage liver disease has become the leading cause of death in these patients, accounting for 50% of all deaths in one study (67). Antiretroviral therapy slows down fibrosis progression and decreases liver-related mortality in HCV-HIV coinfection (68). The indication for treatment in HCV-HIV-coinfected patients is similar to that in monoinfected patients. Whether anti-HCV and anti-HIV therapy should be performed sequentially or simultaneously needs to be decided on an individual basis depending on the stage of HIV disease (as measured by CD4 count). Treatment with PEG IFN and ribavirin results in acceptable SVR rates, with toxicity that is not much different than in HCV monoinfected patients. SVR rates of 43% to 62% in genotypes 2 and 3 infection have been reported after 48 weeks of treatment. Studies evaluating PEG IFN plus ribavirin treatment of HCV genotypes 2 and 3 in HCV-HIV-coinfected patients have reported relapse rates of 32% to 35% when the treatment duration was 24 weeks and the ribavirin dose was 800 mg daily (69,70), although one study (71) using weight-based ribavirin dosing plus PEG IFN reported a relapse rate of 9% with 24 weeks of treatment. In contrast, the relapse rate after 48 weeks of therapy with PEG IFN plus ribavirin 800 mg daily was 3% to 12% (72-74). In genotype 1 infection, the SVR rates were between 16% and 38%. The dose of ribavirin used was 800 mg daily. Patients who fail to achieve either a 2 log drop in viral load after 12 weeks of therapy or undetectable virus have a negligible chance of clearing the virus. Therapy is best provided with close collaboration between an infectious disease specialist and a hepatologist. Simultaneous therapy with ribavirin and didanosine or d4t increases the risk of mitochondrial toxicity (pancreatitis and hyperlactatemia) and should be avoided (75). The combination of zidovudine and ribavirin increases the risk of anemia (76). Therefore, patients on zidovudine who need treatment for hepatitis C should have their HIV therapy changed to eliminate zidovudine if possible.

Recommendation 24: Anti-HCV therapy should be considered in all HCV-HIV-coinfected patients. Patients should be treated with standard doses of IFN and ribavirin for 48 weeks (I). Patients who fail to achieve an EVR should be withdrawn from therapy (I).

Hepatitis C in children

HCV infection seems to progress more slowly to fibrosis and cirrhosis in childhood-acquired disease than in adult-acquired disease (77,78). Standard IFN 3 MU/m^2 three times a week with ribavirin 15 mg/kg/day for 48 weeks yielded an SVR of 40% to 60% overall, and 70% to 100% in genotype 2 or 3 infection (79). PEG IFN-alpha-2a or -2b and ribavirin have been used in small numbers of HCV-infected children with SVR rates of 43% to 59% (higher in genotypes 2 and 3 than in genotypes 1 and 4) (80,81). Whether EVR can be used, as in adults, to stop therapy early in patients destined to be nonresponders is not clear. The tolerability and side effect profile in children and adults appears similar except for transient growth inhibition in children.

While the medical need for therapy seems limited in the majority of HCV-infected children, antiviral therapy may be warranted in selected patients with rapidly progressive fibrosis. The exact indications for therapy remain to be better defined. Therefore, decisions about treatment are best made in specialized centres. A pretreatment liver biopsy should show significant inflammation or fibrosis. Because there are only limited data on the use of PEG IFN and ribavirin, current treatment in children remains to be standard IFN-alpha 3 MU/m^2 subcutaneously three times a week combined with ribavirin 15 mg/kg/day orally. This leads to practical problems with ribavirin dosing with the available preparations in children younger than eight to 10 years of age because ribavirin is only available in 200 mg tablets. Whether antiviral therapy in children carries long-term side effects remains to be seen. Children younger than three years should not be treated because of concerns of potential neurotoxicity of IFN on the developing brain. Furthermore, spontaneous viral clearance occurs with high frequency in this age group.

There is insufficient information to make any specific recommendations about treating children with hepatitis C.

Injection drug users

The prevalence of HCV infection across Canada is highest in injection drug users (greater than 50%) (1,82-86). With more than two-thirds of new HCV infections today occurring through IDU, the relative importance of this patient population for HCV disease and related public health issues will further increase in the future. Injection drug users are difficult to reach with traditional medical care structures and are often psychosocially unstable, with ongoing addiction problems. They frequently have multiple medical and psychiatric comorbidities and social issues (homelessness and lack of supports), are highly mobile and fear prosecution. Given the high prevalence of HCV infection among injection drug users and the central role of this population in the HCV epidemic today, it is not justifiable to automatically exclude HCV-infected injection drug users from antiviral therapy. Although the limited data available indicate that only approximately 10% of HCV-infected injection drug users who are potential candidates for HCV therapy actually get treated (87-90), other data suggest that 70% to 80% express an interest in being treated (88,90). The low rate of uptake of therapy was due to a multitude of medical comorbidities and social problems rather than to a reluctance on the part of physicians to treat these patients. Data on treatment outcome are largely lacking.

Recommendation 25: An appropriately funded, multidisciplinary effort is required to improve care strategies for HCV-infected injection drug users. Antiviral therapy should be considered in selected patients in whom HCV-related morbidity or mortality will likely become relevant (II-2). This requires an integrated multidisciplinary approach reaching beyond traditional care structures.

HEMATOPOIETIC GROWTH FACTOR SUPPORT IN THE MANAGEMENT OF HEPATITIS C

Maximizing response rates to HCV therapy requires full treatment adherence to both PEG IFN and ribavirin. However, anemia due to ribavirin-induced hemolysis is often a limiting factor. Treatment-associated anemia requiring a reduction in the ribavirin dose occurs in 25% of patients, often in the first one to two months of therapy (91,92), and negatively impacts the SVR. Ribavirin-induced anemia is more frequent with the higher doses of ribavirin used to treat nongenotypes 2 and 3 infection. The use of erythropoietin to stimulate red cell production has been investigated. The data clearly show that erythropoietin stimulates a rise in hemoglobin and allows a higher overall ribavirin dose to be given (91-93). These studies were recently extended and showed that the use of erythropoietin allowed higher ribavirin dosing and, thereby, improved SVR compared with a group in which erythropoietin was not used (94).

Treatment with erythropoietin may be considered if the hemoglobin falls by more than 40 g/L, or falls below 110 g/L, or if patients become symptomatic from anemia (eg, weakness, dyspnea and angina). The initial dose should be between 20,000 IU and 40,000 IU subcutaneously per week, increasing to a maximum dose of 60,000 IU per week, if required. Erythropoietin dosing is maintained to keep the hemoglobin at or above 110 g/L, but it is not necessary to aim for a return to the baseline hemoglobin level. Ribavirin-induced anemia also results in an increased consumption of red cell production factors, and thus, supplementation with iron, folic acid and vitamin B12 may be considered. Other causes of anemia need to be ruled out by laboratory testing (ie, iron, folate and vitamin B12) before attributing the anemia to medication.

Although erythropoietin can be useful, there are insufficient data to recommend its routine use in all patients.

Between 30% and 50% of patients experience a fall in neutrophil counts within the first two weeks of therapy (15-18), and neutropenia is the most common cause of IFN dose reduction. Although dose reductions or the addition of granulocyte colony-stimulating factor is commonly recommended when the neutrophil count falls to less than 0.5×10^9/L, this does not seem to be associated with an increased risk of infection (95). Although the package inserts for both PEG IFNs (Pegasys RBV, Hoffmann-La Roche Ltd, Canada; and Pegetron, Schering-Plough Canada Inc) suggest dose reductions if the neutrophil count falls below 0.7×10^9/L and recommend discontinuation if the neutrophil count falls below 0.5×10^9/L, experts suggest that dose reductions are not necessary until the neutrophil count falls below 0.5×10^9/L, with discontinuation if the neutrophil count falls below 0.3×10^9/mL. Because less than optimal doses of IFN have a negative impact on SVR rates, granulocyte colony-stimulating factor has been used to maintain the IFN dose (96). However, there are insufficient data to recommend the use of this agent as a standard of care.

Although the package inserts for both PEG IFNs suggest dose reductions if the platelet count falls below 75×10^9/L and recommend discontinuation if the platelet count falls below 50×10^9/L, experts suggest that dose reductions are not necessary until the platelet count falls below 30×10^9/L, with discontinuation if the platelet count falls below 20×10^9/L.

Recommendation 26: Erythropoietin can be used to support hemoglobin levels in patients on treatment with PEG IFN and ribavirin. However, there is insufficient evidence to recommend its use for all patients (III).

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THE ATTACHED IS EXHIBIT "C" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 13TH DAY OF OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

The 1986-1990 Hepatitis C Claims Centre
Settlement Administrator
PO Box 2370, Station D
Ottawa ON K1P 5W5
Toll free: 1 877 434-0944
Fax: (613) 569-1763
www.hepc8690.ca

DTL

March 11, 2016

Claimant name and claim number

Dear Claimant:

Please note that you may be eligible for further compensation. Compensation may be payable to approved class members who have returned a duly signed Release if they underwent at least one (1) month of Compensable HCV Drug Therapy. **Compensable HCV Drug Therapy strictly means taking Interferon or Ribavirin (alone or in combination).** The *1986-1990 Hepatitis C Settlement Agreement* provides that $1,000 (indexed) is payable for every completed month (and no lesser period) of therapy.

To claim for this compensation, the physician who monitored the HCV Drug Therapy must complete the section below ONLY when six (6) months of HCV Drug Therapy have been completed or the therapy has ended, whichever comes first.

Please return this by mail, using the enclosed self-addressed envelope.

The Physician who prescribed the Compensable HCV Drug Therapy, or the physician who monitored this therapy should complete the section below.

1.	Check one box below and provide the treatment dates for the Compensable HCV Drug Therapy.	Start Date D/M/YYYY	End Date D/M/YYYY
	☐ Interferon therapy	/ /	/ /
	☐ Interferon/Ribavirin combination therapy	/ /	/ /
	☐ Ribavirin	/ /	/ /
	☐ Pegetron	/ /	/ /
	☐ Pegasys	/ /	/ /
	☐ Other (please specify):	/ /	/ /
2.	Indicate the number of completed months of Compensable HCV Drug Therapy.	_____ months	
3.	Is the Compensable HCV Drug Therapy continuing?	☐ Yes	☐ No

Physician's Signature: _____

Date: _____

Telephone: (___) _____

Physician's Stamp

THE ATTACHED IS EXHIBIT "D" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 13TH DAY OF OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver

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RP Myers, H Shah, KW Burak, C Cooper, JJ Feld. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol 2015;29(1):19-34.

Chronic hepatitis C remains a significant medical and economic burden in Canada, affecting nearly 1% of the population. Since the last Canadian consensus conference on the management of chronic hepatitis C, major advances have occurred that warrant a review of recommended management approaches for these patients. Specifically, direct-acting antiviral agents with dramatically improved rates of virological clearance compared with standard therapy have been developed and interferon-free, all-oral antiviral regimens have been approved. In light of this new evidence, an update to the 2012 Canadian Association for the Study of the Liver consensus guidelines on the management of hepatitis C was produced. The present document reviews the epidemiology of hepatitis C in Canada, preferred diagnostic testing approaches and recommendations for the treatment of chronically infected patients with the newly approved antiviral agents, including those who have previously failed peginterferon and ribavirin-based therapy. In addition, recommendations are made regarding approaches to reducing the burden of hepatitis C in Canada.

Key Words: *Dasabuvir; Direct-acting antivirals; Guideline; Hepatitis C; Interferon; Ledipasvir; Ombitasvir; Paritaprevir; Peginterferon; Simeprevir; Sofosbuvir; Ribavirin; Therapy; Treatment*

Mise à jour sur la prise en charge de l'hépatite C chronique : les lignes directrices consensuelles 2015 de l'Association canadienne pour l'étude du foie

L'hépatite C chronique demeure un fardeau médical et économique important au Canada, car il touche près de 1 % de la population. Depuis la dernière conférence consensuelle canadienne sur la prise en charge de l'hépatite C chronique, on a réalisé des progrès marqués qui justifient une analyse des démarches de prise en charge recommandées. Notamment, on a mis au point des antiviraux à action directe au taux de clairance virologique bien supérieur à celui du traitement standard et on a homologué des antiviraux sans interféron par voie orale. À la lumière de ces nouvelles données probantes, l'Association canadienne pour l'étude du foie a mis à jour les lignes directrices consensuelles 2012 sur la prise en charge de l'hépatite C. Le présent document traite de l'épidémiologie de l'hépatite C au Canada, des démarches et des recommandations favorisées pour traiter les patients atteints d'une infection chronique à l'aide des nouveaux antiviraux homologués, y compris les patients qui n'avaient pas répondu à un traitement à l'interféron pégylé et à la ribavirine. Il contient également des recommandations sur les approches pour réduire le fardeau de l'hépatite C au Canada.

The present guidelines were written to assist physicians and other health care professionals in the management of patients with chronic hepatitis C virus (HCV) infection. They were drafted by Canadian HCV experts at the request of the Executive Committee of the Canadian Association of the Study of the Liver (CASL). The document was made available for review by CASL members and a revised draft based on this feedback was submitted to the Executive Committee of CASL for approval. The information contained within the present guidelines represents a synthesis of evidence from the published literature and scientific abstract presentations available at the time of writing with supplementation by the expert opinions of the authors. Any recommendations should be considered preferred approaches to care rather than strict standards. In some cases, off-label use of regimens are recommended based on the authors' opinions. To more fully characterize the quality of evidence supporting these recommendations, we have assigned a class (reflecting benefit versus risk) and level (assessing strength of certainty) of evidence as adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (1,2), and as used in similar practice guidelines of CASL (3) and the American Association for the Study of Liver Diseases (4) (Table 1). No funding was provided to the authors for this work.

Since the last update of the CASL management guidelines for chronic hepatitis C (CHC) in 2012 (3), major advances have occurred including: the approval of novel direct-acting antiviral agents (DAAs) used with pegylated interferon (PEG-IFN) that have improved efficacy and tolerability compared with first-generation DAAs and/or standard PEG-IFN-based therapy (5-7); and the approval of all-oral, IFN-free, DAA combination therapies with markedly improved efficacy and tolerability and activity beyond just HCV genotype 1 (5,8-15). The current document was developed as an update to previous guidelines with a focus on the management of HCV-infected patients rather than an exhaustive review of CHC or HCV screening. Future guidelines will include 'special populations' with CHC, including people who use injection drugs (PWIDs), incarcerated individuals, patients with decompensated cirrhosis, those pre- or post-transplantation, and patients with HIV/HCV coinfection (for whom relevant guidelines have recently been published by the Canadian Institute of Health Research HIV Trials Network) (16). Due to the rapidity of advances in this field, recommendations in the present document will be updated regularly as new information emerges and novel agents are approved.

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TABLE 1
Grading system for recommendations

Classification	Description
Class of evidence	
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful and effective
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class 2a	Weight of evidence/opinion is in favour of usefulness/efficacy
Class 2b	Usefulness/efficacy is less well established by evidence/opinion
Class 3	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful
Grade of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinions of experts, case studies or standard-of-care

EPIDEMIOLOGY OF HEPATITIS C IN CANADA

CHC remains a significant medical and economic burden in Canada (17-19). In the Canadian Health Measures Survey (20), Statistics Canada and the Public Health Agency of Canada reported an estimated anti-HCV prevalence of 0.5% (95% CI 0.3% to 0.9%) or approximately 138,600 (95% CI 55,800 to 221,300) anti-HCV-positive individuals in Canada. However, these figures are likely underestimates because the Canadian Health Measures Survey excluded several high-risk populations including incarcerated individuals, Aboriginals and PWIDs (20). In fact, a recent modelling study suggests that approximately 252,000 Canadians (uncertainty interval 178,000 to 315,000) were chronically infected in 2013 (18). The peak prevalence was estimated to have occurred in 2003, with approximately 260,000 infected individuals. It has been estimated that approximately 60% of HCV cases in Canada are among current or former PWIDs, 20% are among infected immigrants and 11% have received contaminated blood products (21). Of the nearly 8000 incident cases in Canada in 2007, approximately 80% likely occurred via sharing of injecting equipment, and most of the remainder among immigrants from endemic countries (21). There is wide variation in estimates of the number of HCV-infected individuals who remain undiagnosed. Modelling data from the Public Health Agency of Canada estimated that 79% of individuals were diagnosed in 2003 (21); however, the CMHS found that only 30% of anti-HCV-positive individuals were aware of their infection (20).

Genotype 1 infection is the most prevalent genotype in Canada, representing 65% of infected individuals (56% genotype 1a, 33% genotype 1b, and 10% with an unspecified subtype or mixed infection) (22). The genotype 1 subtype is of relevance for some of the new antiviral regimens due to differing efficacy between genotypes 1a and 1b. Genotypes 2 and 3 account for approximately 14% and 20% of infections in Canada, respectively, whereas genotypes 4, 5 and 6 are very rare (<1% of all infections) (22).

Although the overall prevalence of CHC is declining, complications of CHC are increasing due to aging of the infected population and progression of liver fibrosis (17-19). Modelling data suggest that by 2035, cases of decompensated cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality will increase by 80%, 205% and 160%, respectively, compared with 2013 levels (Figure 1) (18). Similarly, annual direct costs associated with CHC (excluding the cost of antiviral therapies) are expected to rise from an estimated $161 million in 2013 to >$258 million at the peak in 2032 (18). Given the alarming estimates of future disease burden, more accurate information regarding the incidence and prevalence of CHC and its sequelae is required to inform health care planning and the allocation of resources. The identification of undiagnosed cases and the dissemination of effective antiviral therapies should be prioritized to reduce complications of this disease (23).

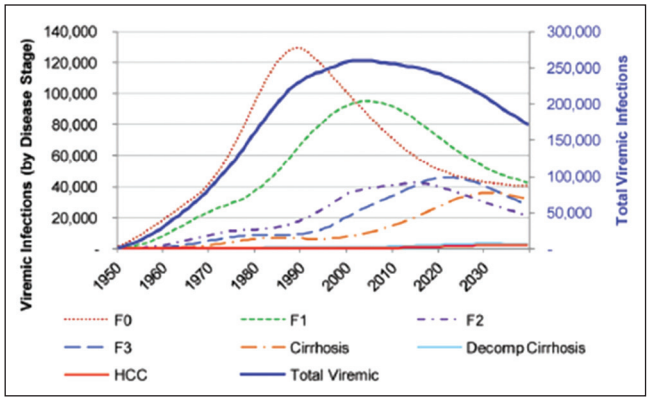

Figure 1) *Modelled incidence of hepatitis C-related sequelae in Canada, 1950 to 2035. Estimates are not mutually exclusive. Reproduced with permission from Myers et al (18). Decomp Decompensated; HCC Hepatocellular carcinoma*

Recommendations:

1. A large population-based seroprevalence survey should be conducted to accurately define the prevalence of hepatitis C in Canada. The design of the study should include populations with an increased risk of hepatitis C, particularly PWIDs, incarcerated individuals and immigrants from endemic countries (Class 2a, Level C).
2. To reduce the future burden of HCV-related morbidity and mortality in Canada, strategies for case identification, harm reduction and disease management – including but not limited to antiviral therapy – should be developed and implemented (Class 2a, Level C).

ANTIVIRAL THERAPY

The primary objective of anti-HCV therapy is complete eradication of the virus, termed a sustained virological response (SVR). SVR has traditionally been defined as undetectable serum HCV RNA at least 24 weeks following the end of treatment (SVR24) (24); however, recent data suggest that earlier assessment at 12 weeks after treatment (SVR12) is sufficient to define this outcome (25). Once achieved, an SVR is considered to be a long-term cure of the virus because late relapses are rare (26,27). SVR is associated with long-term health benefits including improved quality of life (28,29), extrahepatic manifestations of HCV (eg, cryoglobulinemic vasculitis) (30), liver histology (31,32), HCC incidence (33), liver-related morbidity and mortality (34-36), and all-cause mortality (33).

The landscape of antiviral treatment for hepatitis C is changing rapidly. Until recently, the standard therapy was the combination of PEG-IFN and ribavirin (RBV), usually administered for 48 weeks in patients with genotype 1, 4, 5 and 6, and 24 weeks in those with genotypes 2 and 3 (3). Dual therapy achieves SVR rates of 40% to 50% in patients with genotype 1 and approximately 80% in those with genotypes 2, 3, 5 and 6. Results for HCV genotype 4 are intermediate (3). In 2011, the first DAAs, boceprevir (BOC) and telaprevir (TVR), were approved for treatment of HCV genotype 1 in combination with PEG-IFN and RBV. These nonstructural (NS) 3/4A protease inhibitors (PIs) substantially increase rates of SVR in both treatment-naive and previously treated patients compared with dual therapy (37-41). However, they are associated with significant toxicity, complex regimens involving response-guided therapy (RGT), drug-drug interactions (DDIs), and low response rates in patients with cirrhosis and previous treatment failures. In addition, BOC and TVR required coadministration with PEG-IFN and RBV for 24 to 48 weeks, markedly increased the cost of therapy, and are associated with the emergence of resistance-associated variants (RAVs) in the majority of patients who fail treatment (3). The subsequent approval of DAAs with improved efficacy and tolerability, shorter treatment durations, and the option of PEG-IFN- and RBV-free therapy, represents a major advance in the field.

The treatment of CHC is complex and resource intensive. Contributing factors include the high prevalence of psychiatric comorbidities in HCV-infected individuals (eg, depression and addictions), multiple modes of drug administration, side effects, and the requirement for careful on-treatment monitoring of symptoms and laboratory tests. The most successful model to deliver comprehensive CHC care is via a multidisciplinary approach including experienced physicians, nurses and allied health professionals (eg, psychologists, psychiatrists, addiction specialists and social workers). Currently in Canada, a relatively small number of physicians treat CHC, leading in some cases to prolonged wait times for patients to be adequately evaluated and treated. These deficiencies in access to care are greater in rural and remote communities, despite a high HCV prevalence in many regions with limited health care capacity. Moreover, public funding for treatment nurses – who have represented a vital component of the management team – is not universally available. To achieve a meaningful reduction in the future burden of CHC, it will be vital to expand treatment capacity via additional training and funding of experienced personnel and enhanced access to publically funded antiviral therapies (42). With the advent of all-oral antiviral regimens that have few contraindications, minimal toxicity and short treatment courses, the number of patients that can be treated should increase dramatically. However, team-based management will still be necessary to achieve this goal.

Recommendation:

3. Increased resources are necessary to improve hepatitis C treatment capacity in Canada, including the training of expert treaters and public funding for treatment nurses (Class 2a, Level C).

INDICATIONS AND CONTRAINDICATIONS TO ANTIVIRAL TREATMENT

All patients with CHC should be considered candidates for antiviral treatment. The decision of if and when to initiate therapy should be based on the balance between the perceived benefits and risks of treatment and the wishes of the individual patient. Factors to consider include the probability of SVR and the likelihood of progression to advanced liver disease without viral eradication, the presence of extrahepatic manifestations of CHC, the patient's anticipated tolerability of treatment and the life expectancy of the patient. The prospect of new therapies with expected benefits over currently available treatments should also be considered. In light of these issues, prompt initiation of treatment should be considered in certain patient subgroups, especially those with advanced liver fibrosis (F3 or F4 according to the METAVIR classification [bridging fibrosis or cirrhosis]) (43). These patients are at the highest risk of HCV-related complications including liver failure and HCC. Treatment of patients with mild to moderate fibrosis (F1 or F2) should also be considered because progression to more advanced stages is associated with a reduced likelihood of SVR. Moreover, viral eradication in patients at risk of infecting others (eg, PWIDs who continue to share injecting equipment) may reduce the incidence of new infections (44). The curative nature of HCV therapy means that those who achieve SVR before developing cirrhosis do not require long-term follow-up. There are additional benefits to SVR beyond liver disease prevention, including improved quality of life (28,29) and a reduction in all-cause mortality (33). Patients with extrahepatic manifestations of CHC including cryoglobulinemic vasculitis, porphyria cutanea tarda and glomerulonephritis should be considered for treatment regardless of their underlying liver disease severity because these conditions typically respond to viral eradication (30).

TABLE 2
Contraindications for treatment with peginterferon and ribavirin

Absolute contraindications	Pregnancy
Strong, but not absolute, contraindications	Alcohol abuse
	Hepatic decompensation
	Coronary artery disease
	Solid organ transplantation (except liver)
Relative contraindications	Major depression
	Major psychosis
	Autoimmune disease
	Injection drug use
	Renal failure (including dialysis)
Contraindications that are no longer contraindications	Normal alanine aminotransferase
	Stable methadone maintenance
	Neutropenia, anemia or thrombocytopenia
	Controlled seizure disorder
	Older than 65 years of age
	Alcohol use

Table reproduced with permission from (3)

There are very few absolute contraindications to treatment with PEG-IFN- and RBV- based therapy. As postmarketing experience with these therapies has grown, many conditions previously regarded as absolute contraindications are now considered relative, and some may be present only temporarily (Table 2) (3). In most cases, treatment of these patients with PEG-IFN and RBV requires considerable expertise and, therefore, patients with relative contraindications should be treated in expert centres. Contraindications to the recently approved, all-oral regimens are distinctly uncommon.

Recommendations:

4. All patients with chronic HCV infection should be considered candidates for antiviral therapy (Class 1, Level A).
5. Antiviral treatment should be strongly considered in patients with evidence of liver fibrosis (Class 1, Level A).
6. Patients with extrahepatic manifestations of HCV should be considered for antiviral therapy (Class 1, Level A).

PRETREATMENT ASSESSMENT

Routine assessment

The routine assessment of HCV-infected patients should include risk factors for viral acquisition (eg, injection drug use, receipt of potentially contaminated blood products or tissues, and origin from a high-prevalence region), signs and symptoms of advanced liver disease (eg, jaundice, ascites, encephalopathy, portal hypertension-related hemorrhage) or extrahepatic manifestations of CHC, presence of cofactors that may accelerate disease progression (eg, alcohol use, obesity,

TABLE 3
Routine testing of patients with chronic hepatitis C virus (HCV)*

Category of Testing	Tests	Comments
Confirmation and characterization of chronic infection	HCV RNA	Confirms chronicity and baseline for treatment responses
	HCV genotype and subtype	Directs choice of treatment regimen
Assessment of liver disease	Complete blood count	Thrombocytopenia may indicate cirrhosis and portal hypertension. Platelets needed for APRI calculation
	Alanine aminotransferase	Normal value does not preclude significant fibrosis
	Asparatate aminotransferase	Asparatate aminotransferase needed for calculation of APRI
	Gamma-glutamyl transferase	
	Alkaline phosphatase	
	Bilirubin	Elevated bilirubin or INR, or hypoalbuminemia may indicate significant liver dysfunction
	INR (or prothrombin time)	
	Albumin	
	Creatinine	Renal dysfunction increases ribavirin-related hemolytic anemia and may impact drug pharmacodynamics
	Abdominal ultrasound	May suggest cirrhosis, in which case, serves as a baseline for hepatocellular carcinoma surveillance
Viral coinfections	Immunoglobulin G anti-HAV	If negative, vaccinate against hepatitis A
	HBsAg	Exclude hepatitis B coinfection
	Hepatitis B surface antibody	If negative (and HBsAg-negative), vaccinate against hepatitis B
	anti-HIV	Exclude HIV coinfection
Exclude other causes of liver disease†	Alpha-1-antitrypsin	Alpha-1-antitrypsin deficiency
	Ceruloplasmin	Wilson disease.
	Ferritin, serum iron, total iron-binding capacity	Iron overload
	Antinuclear antibody	Autoimmune hepatitis
	Smooth muscle antibody	
	Antimitochrondrial antibody	Primary biliary cirrhosis
	Immunoglobulin G	Often elevated in autoimmune hepatitis and cirrhosis of any cause
	Immunoglobulin A	Often elevated in fatty liver and alcoholic liver disease
	Immunoglobulin M	Often elevated in primary biliary cirrhosis
Contraindications to treatment	Serum or urine β-human chorionic gonadotropin	Exclude pregnancy in women of reproductive age
	Electrocardiogram	If >50 years of age or history of cardiac disease
	Thyroid-stimulating hormone	Exclude thyroid disease, which may be exacerbated by interferon
	Fundoscopy	Exclude retinopathy in patients >50 years of age or with hypertension or diabetes mellitus if interferon is to be prescribed

**Confirmed anti-HCV antibody positive; †Suggested tests only. Tailor testing to individual case. Anti-HAV Antibodies to hepatitis A virus; APRI Aspartate aminotransferase/platelet ratio index; HBsAg Hepatitis B surface antigen; INR International normalized ratio*

coinfections) and potential contraindications to IFN-based therapy (Table 2), which would favour the use of an IFN-free regimen. Necessary laboratory testing includes virological tests to confirm and characterize HCV infection, liver biochemistry, abdominal ultrasound, an assessment of fibrosis stage and tests to rule out coinfections, direct appropriate vaccination and identify contraindications to treatment. In patients with abnormal liver biochemistry, serological tests to exclude coexisting liver diseases should be considered (Table 3).

Virological testing

Approximately one-quarter of patients infected with HCV will clear the virus spontaneously (45). Therefore, chronic HCV infection must be confirmed in all anti-HCV-positive individuals using a sensitive HCV RNA test. HCV RNA detection and quantification using real-time polymerase chain reaction assays is standard due to their sensitivity, specificity, accuracy and broad dynamic range. Results should be expressed in IU/mL and normalized to the WHO international standard. Quantitative assays with a lower limit of detection of approximately 10 IU/mL to 15 IU/mL are recommended. HCV RNA test results should be available within a timely fashion (within seven days) to facilitate management decisions. The rapid identification of failing treatment will reduce patient exposure to costly therapies and potential toxicity, and likely limit the development of RAVs.

The HCV genotype should be assessed in all patients because it has important implications for the decision to initiate treatment and the choice of regimen. With PEG-IFN and RBV therapy, knowledge of only the main genotype (1 to 6) was necessary. However, knowledge of the subtype is now critical, particularly for genotype 1, because of the differing genetic barriers to resistance of HCV subtypes 1a and 1b for many classes of DAAs (46,47). For some DAAs, additional testing (eg, for the Q80K polymorphism [see below]) and/or alternative treatment based on subtype (eg, the use of RBV) may be required.

Recommendations:

7. HCV RNA, genotype, and subtype testing (ie, 1a versus 1b) are essential to the management of patients with chronic hepatitis C (Class 1, Level A).
8. HCV RNA testing should be performed using a sensitive quantitative assay (lower limit of detection of ≤10 IU/mL to 15 IU/mL) with a broad dynamic range. Standardized results should be expressed in IU/mL and be available within a maximum of seven days to facilitate management decisions (Class 1, Level A).

Assessment of liver disease severity

Assessment of the severity of hepatic fibrosis is vital for determining the prognosis of HCV-infected patients and the necessity of antiviral treatment. Identification of patients with cirrhosis is particularly important due to their increased risk of hepatic complications, reduced

likelihood of treatment response, and their requirement for surveillance for HCC and esophageal varices. Although the diagnosis of cirrhosis is obvious in some cases based on routine tests (eg, a nodular shrunken liver, splenomegaly or portal hypertensive collaterals on ultrasound), traditionally, liver biopsy has been the reference method for staging fibrosis, determining the severity of other histological lesions (eg, necroinflammation, steatosis) and ruling out coexistent liver diseases (eg, iron overload). Various validated scoring systems have demonstrated sufficient reproducibility and interobserver variability to justify clinical use (eg, METAVIR, Scheuer, Ishak, and Knodell's Hepatic Activity Index) (48). However, liver biopsy has several limitations, including invasiveness and the potential for serious complications including hemorrhage (approximately one in 1000) and death (approximately one in 10,000) (49,50), sampling error and variability in pathological interpretation, high cost, limited availability in many centres, and the difficulty of repeating biopsies to monitor temporal changes in fibrosis. In light of these limitations, numerous noninvasive alternatives to biopsy have been developed (51) including serum markers (eg, the aspartate aminotransferase/platelet ratio index [52]), FibroTest (FibroSure, LabCorp, USA) (53), transient elastography (TE; FibroScan, Echosens, France) (54-57) and other imaging-based tools (58,59).

Although not universally available, a wealth of literature has confirmed that these noninvasive tools can be used instead of liver biopsy to stage HCV-related fibrosis at acceptable levels of accuracy and reproducibility. In a recent survey of Canadian specialists who manage patients with chronic liver disease (60), TE was the primary mode of fibrosis assessment in HCV-infected individuals in 53% of respondents, followed by liver biopsy in 37%. Nearly one-half of respondents estimated that these noninvasive alternatives have reduced their use of liver biopsy by over 50%. In general, these tests are highly accurate for diagnosing cirrhosis and have acceptable, but lower, performance for moderate to severe fibrosis (F2 or greater). The identification of mild fibrosis (F1) and the differentiation between individual stages is poor; however, these limitations also apply to liver biopsy. Emerging data have also demonstrated a correlation between these tests and HCV-related clinical outcomes (61-63), their cost-effectiveness compared with biopsy (64) and responsiveness to viral eradication (65,66). Future studies are necessary to determine the minimal clinically important changes in these markers to facilitate serial monitoring of fibrosis.

Recommendations:

9. Liver fibrosis assessment is vital to the management of patients with CHC (Class 1, Level A).
10. Acceptable methods of fibrosis assessment include liver biopsy, TE (FibroScan) and serum biomarker panels (eg, FibroTest), either alone or in combination. All jurisdictions should provide access to at least one accurate, noninvasive method to assess fibrosis (Class 1, Level A).
11. Alternatively, cirrhosis can be confidently diagnosed in some patients with clear clinical or radiographic evidence (Class 2a, Level C).

Utility of interleukin 28B testing

Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) near the interleukin 28B (IL28B) gene on chromosome 19 that are strongly associated with both spontaneous and treatment-induced HCV clearance (67-70). Patients with the favourable CC genotype at rs12979860 have a more than twofold likelihood of spontaneous HCV clearance compared with heterozygotes (CT) and homozygotes (TT) (67). The CC genotype is also associated with an approximately twofold increase in SVR to PEG-IFN and RBV therapy compared with the unfavourable SNPs in patients with HCV genotype 1 (68,70). The relevance in genotypes 2 and 3 and in treatment-experienced patients is less clear. There is marked ethnic variation in the prevalence of the IL28B genotypes.

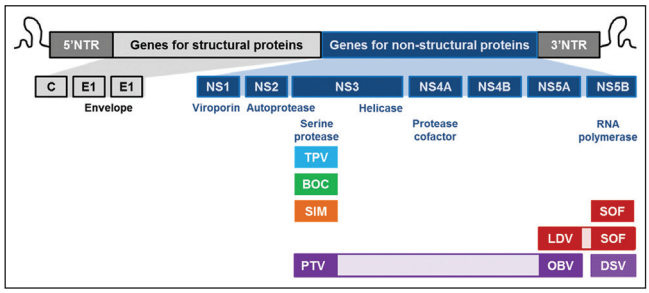

Figure 2) *Hepatitis C virus genome and the polyprotein targets of newly approved, direct-acting antiviral agents. Note: Sofosbuvir (SOF) is a nucleotide nonstructural protein (NS)5B polymerase inhibitor and dasabuvir (DSV) is a non-nucleoside polymerase inhibitor. BOC Boceprevir; LDV Ledipasvir; OBV Ombitasvir; PTV Paritaprevir; SIM Simeprevir; TPV Telaprevir*

The CC genotype is highly prevalent in Asians, but relatively uncommon in Africans, while Caucasians and Hispanics have an intermediate prevalence (68). Similar associations have been reported for the rs8099917 SNP (favourable allele = T and unfavourable allele = G) (71), and for the recently described IFN-lambda 4 (IFNL4) SNP ss46915590 (favourable allele = T and unfavourable allele = ΔG) (72). For simplicity, further discussion will refer to the rs12979860 SNP.

The impact of the IL28B genotype on treatment success is lower when treatment includes DAAs. Patients with the CC genotype have a very high rate of SVR when treated with DAAs plus PEG-IFN and RBV, reaching 98% with sofosbuvir (SOF)-based triple therapy for HCV genotype 1 (5). DAAs lead to a greater relative increase in SVR in non-CC patients. While the IL28B genotype is of limited importance with respect to SVR rates with IFN-free regimens (8,15), whether patients with the favourable IL28B genotype will be able to shorten therapy or use fewer DAAs is unclear.

Recommendations:

12. The IL28B genotype may provide valuable information regarding the likelihood of SVR depending on the HCV genotype and therapy under consideration (Class 2b, Level A).
13. A nonfavourable IL28B genotype does not preclude antiviral therapy (Class 1, Level A).

DAAs

Multiple steps in the HCV life cycle have proven attractive targets for novel pharmacological therapies (Figure 2). Particularly promising agents target the NS3/4A serine protease, the NS5B RNA-dependent RNA polymerase and the NS5A protein (73). The first DAAs approved by Health Canada for the treatment of HCV genotype 1 were the NS3/4A PIs, BOC and TVR. A second-generation PI, simeprevir (SIM), was approved in 2013 for use in combination with PEG-IFN and RBV for genotype 1. In 2013, the first HCV nucleotide polymerase inhibitor, SOF, was approved for use in combination with PEG-IFN and RBV for genotypes 1 and 4 and with RBV alone for genotypes 2 and 3. In 2014, the single-tablet regimen of SOF combined with the NS5A inhibitor ledipasvir (LDV) was approved for patients with HCV genotype 1, including those previously treated with BOC and TVR. In addition, the combination of the ritonavir-boosted PI paritaprevir (PTV_R), the NS5A inhibitor ombitasvir (OBV), and the non-nucleoside polymerase inhibitor dasabuvir (DSV) with or without RBV was approved for patients with HCV genotype 1. Given the markedly improved efficacy and tolerability of these regimens, all patients would benefit from IFN-free therapy. Therefore, these newly approved agents are recommended as first-line therapy for all indications throughout these guidelines. However, access to IFN-free regimens is not universal across Canada. Whether to initiate therapy with an IFN-containing regimen or wait for the availability of all-oral regimens is an individualized decision that must

consider the patient's wishes, the urgency of therapy, the severity of liver disease, the anticipated tolerability of PEG-IFN, the likelihood of SVR and the expected timeline for access to IFN-free regimens.

TREATMENT-NAIVE PATIENTS WITH HCV GENOTYPE 1 (TABLE 4)

PEG-IFN-free regimens

SOF/LDV: The nucleotide polymerase inhibitor SOF (400 mg) has been combined with the NS5A inhibitor LDV (90 mg) in a single tablet regimen (SOF/LDV) administered once daily. This combination was evaluated in treatment-naive patients in the open-label ION-1 (8) and ION-3 (10) phase 3 trials with a primary end point of SVR12. In the ION-1 study, which included patients with compensated cirrhosis (16%), participants were randomly assigned to 12 or 24 weeks of SOF/LDV with or without weight-based RBV (8). Among patients who received SOF/LDV for 12 weeks, SVR12 rates were 97% (211 of 217) and 99% (211 of 214) in those who received and did not receive RBV, respectively. In the 24-week treatment arms, SVR12 rates were 99% (215 of 217) in RBV-treated patients compared with 98% (212 of 217) in those who received SOF/LDV alone. There were no statistically significant differences between treatment arms or pretreatment characteristics that were predictive of response. Among the 136 cirrhotic patients, SVR12 rates ranged from 94% to 100%, with no differences between 12 and 24 weeks or with or without RBV. The IL28B genotype was not predictive of response; SVR12 rates ranged from 97% to 99% among patients with the unfavourable non-CC genotype. Only one patient experienced virological breakthrough on therapy and two patients relapsed. All three of these patients had NS5A resistance, but no SOF resistance was detected by deep sequencing. Although the majority of patients complained of at least one adverse event, 93% were mild to moderate in severity with the most common being fatigue, headache, insomnia and nausea. Adverse events were more common in patients randomized to receive RBV. No patient receiving SOF/LDV alone had a hemoglobin concentration <100 g/L.

In the ION-3 study (10), treatment-naive, noncirrhotic patients with HCV genotype 1 were randomly assigned to eight weeks of SOF/LDV with or without weight-based RBV, or SOF/LDV alone for 12 weeks. Among the 215 patients randomly assigned to SOF/LDV for eight weeks, 202 (94%) achieved SVR12, compared with 201 of 216 (93%) who received SOF/LDV/RBV for eight weeks, and 206 of 216 (95%) who received SOF/LDV for 12 weeks. The relapse rates were 5% (SOF/LDV) and 4% (SOF/LDV/RBV) in the eight-week treatment arms and 1% in the 12-week treatment arm. Although the 12-week regimen had a lower relapse rate, treating all patients for an additional four weeks would lead to overtreatment of the majority of individuals. Therefore, a post hoc analysis of baseline viral load was conducted to identify patients in whom an eight-week regimen would suffice (74). In this analysis, patients with an HCV RNA level <6 million IU/mL had a 2% relapse rate in both the eight-week (two of 123) and 12-week (two of 131) SOF/LDV treatment arms, and SVR12 rates of 97% (119 of 123) and 96% (126 of 131), respectively. However, in patients with a baseline viral load ≥6 million IU/mL, those treated for only eight weeks with SOF/LDV had a 10% (nine of 92) relapse rate versus only 1% (one of 85) if treated for 12 weeks. Corresponding SVR12 rates were 90% (83 of 92) and 94% (80 of 85), respectively. Based on these findings, Health Canada and the United States Food and Drug Administration (FDA) have recommended an eight-week regimen of SOF/LDV in treatment-naive, noncirrhotic patients with baseline HCV RNA <6 million IU/mL and 12 weeks in patients with a higher viral load (74).

In addition to baseline viral load, the impact of baseline RAVs on treatment response was examined (10). Although 15 of 23 relapsers (65%) to SOF/LDV had NS5A-resistant variants detected at the time of relapse (present at baseline in nine patients), SOF resistance was not identified. Among 116 patients (18%) with NS5A resistance at baseline, 90% achieved SVR12, suggesting a minimal impact of baseline NS5A RAVs on treatment response with SOF/LDV.

Recommendations:

14. In noncirrhotic, treatment-naive patients with HCV genotype 1, SOF/LDV should be given for eight weeks (Class 1, Level B).
15. In noncirrhotic, treatment-naive patients with genotype 1 and baseline HCV RNA ≥6 million IU/mL, extension of SOF/LDV therapy to 12 weeks can be considered (Class 1, Level C).
16. In cirrhotic, treatment-naive patients with genotype 1, SOF/LDV should be given for 12 weeks (Class 1, Level B).

PTV_R/OBV/DSV ± RBV: The PI PTV is given with low-dose ritonavir (PTV_R) to permit once-daily dosing. PTV_R (150 mg/100 mg) and the NS5A inhibitor OBV (25 mg) are coformulated in a single tablet taken as two tablets once daily. This tablet is combined with the nonnucleoside polymerase inhibitor DSV (250 mg) taken as one tablet twice daily. Placebo or the combination of the three DAAs plus ritonavir (referred to as the '3D' regimen) and weight-based RBV was given for 12 weeks to treatment-naive, noncirrhotic patients with HCV genotype 1 in the phase 3 SAPPHIRE-I trial (15). Patients randomly assigned to placebo subsequently received active treatment. Of 473 patients who started active therapy, 455 (96%) achieved SVR12, clearly superior to a historical control of TVR-based triple therapy in a similar patient population (estimated SVR12 of 78%). SVR12 did

TABLE 4
Treatment-naive patients with hepatitis C virus (HCV) genotype 1

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 1a, noncirrhotic	SOF/LDV × 8–12 weeks*	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24 weeks (if Q80K–)	PEG/RBV/BOC or TVR
				SIM/PEG/RBV × 24 weeks (if Q80K+)
Genotype 1b, noncirrhotic	SOF/LDV × 8–12 weeks*	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV × 12 weeks		SIM/PEG/RBV × 24 weeks	PEG/RBV/BOC or TVR
Genotype 1a, cirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24–48 weeks (if Q80K–)	PEG/RBV/BOC or TVR
				SIM/PEG/RBV × 24 weeks (if Q80K+)
Genotype 1b, cirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24 weeks	PEG/RBV/BOC or TVR

**In noncirrhotic, treatment-naive patients with HCV genotype 1a or 1b, treat with sofosbuvir/ledipasvir (SOF 400 mg/LDV 90 mg) once daily (one tablet) for eight weeks. Consider 12 weeks of treatment if baseline HCV RNA ≥6 million IU/mL. + Positive; – Negative; BOC Boceprevir; DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; Q80K Simeprevir-associated resistance variant at position 80; RBV Ribavirin (weight-based dosing: 1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg); SIM Simeprevir (150 mg once daily); SOF Sofosbuvir (400 mg once daily); TVR Telaprevir*

not differ between patients with HCV genotype 1a (95% [307 of 322]) or 1b (98% [148 of 151]). The only baseline factor associated with response was body mass index (BMI). Obese patients (BMI ≥30 kg/m^2) had an SVR12 rate of 91.5% compared with 97% in patients with a lower BMI. There was no difference in response according to IL28B genotype, fibrosis stage, baseline HCV RNA level, ethnicity or RBV dose modification.

Safety of the regimen was evaluated by comparing with patients randomly assigned to placebo (15). Adverse events were more common in those on active treatment (88%); however, 73% of placebo-treated patients also experienced at least one adverse event. Severe adverse events (2.1%), in particular those requiring drug discontinuation (<1%), were rare. The most common side effects were fatigue and headache, but were no more frequent with active treatment than placebo. Nausea, pruritus, insomnia, diarrhea and asthenia were reported more frequently in patients on active treatment. Total bilirubin elevations were seen in 2.8% of patients on this regimen, likely due to RBV-related hemolysis and inhibition of the bilirubin transporters OATP1B1 and OATP1B3 by PTV_R. No episodes of hepatotoxicity were reported. Grade 2 anemia (hemoglobin 80 g/L to 100 g/L) was reported in 5.8% of patients treated with this regimen including RBV. In 5.5% of patients, the RBV dose was modified due to adverse events, but no impact on the rate of SVR12 was observed in these patients.

The TURQUOISE-II phase 3 trial evaluated the PTV_R/OBV/DSV plus RBV regimen (12 versus 24 weeks) in treatment-naive and treatment-experienced patients with compensated cirrhosis (13). Among treatment-naive patients, the rates of SVR12 were similar between the 12- and 24-week arms (94% [81 of 86] versus 95% [70 of 74]) and by genotype subtype (genotype 1a: 12 versus 24 weeks: 92% [59 of 64] versus 93% [52 of 56]; and genotype 1b: 100% in both the 12-week [22 of 22] and 24-week [18 of 18] groups). SVR12 rates among previously treated patients from TURQUOISE-II are discussed below.

To evaluate the importance of RBV administration with PTV_R/OBV/DSV, the PEARL-III and PEARL-IV phase 3 trials were conducted in treatment-naive, noncirrhotic patients with genotypes 1b and 1a, respectively (75). In PEARL-III, patients with HCV genotype 1b were randomly assigned to receive PTV_R/OBV/DSV alone (n=209) or with RBV (n=210) for 12 weeks. Only three of 419 patients in the trial failed treatment; the SVR12 rate was 99% in both groups. In the PEARL-IV trial, of 205 patients with HCV genotype 1a randomly assigned to receive PTV_R/OBV/DSV alone for 12 weeks, 185 (90%) achieved SVR12; this rate was significantly lower than that observed in patients treated with PTV_R/OBV/DSV plus RBV (97% [97 of 100]), emphasizing the importance of RBV coadministration when this regimen is prescribed to patients with HCV genotype 1a (75).

Recommendations:

17. In treatment-naive patients with HCV genotype 1a infection, with or without cirrhosis, and for those with genotype 1b infection and cirrhosis, coformulated PTV_R/OBV/DSV should be given with weight-based RBV for 12 weeks (Class 1, Level A).
18. In noncirrhotic, treatment-naive patients with genotype 1b infection, coformulated PTV_R/OBV/DSV should be given without RBV for 12 weeks (Class 1, Level A).

SOF and SIM: SOF (400 mg daily) was combined with the second-generation PI SIM (150 mg daily) with or without RBV for 12 or 24 weeks in the phase 2 COSMOS study (76). The study was divided into two cohorts: cohort 1 included 80 null responders with mild fibrosis (F0 to F2) and cohort 2 included 87 treatment-naive and null responders with advanced fibrosis (F3 and F4). HCV RNA was suppressed on treatment in all patients, but six patients relapsed. The overall SVR12 rate was 92% (154 of 167), with similar results in cohorts 1 and 2 (90% [72 of 80] versus 94% [82 of 87], respectively). The SVR12 rates did not differ between 12 and 24 weeks of treatment, with or without RBV, or in treatment-naive versus treatment-experienced patients (95% [38 of 40] versus 91% [116 of 127]). The presence of a polymorphism at position 80 with a substitution of a K (lysine) for Q (glutamine), referred to as the 'Q80K' polymorphism, which is associated with reduced activity of SIM and found almost exclusively in patients with HCV genotype 1a (see below) (77,78), did not impact the rate of SVR12 (76). Although four of the six relapsers had genotype 1a infection and the Q80K polymorphism at baseline, 88% (51 of 58) of patients with this polymorphism still achieved SVR12. In this small trial, the regimen was well tolerated; headache, fatigue and nausea were the most commonly reported side effects. Only four patients (2%) discontinued treatment due to adverse events. Although the results from this trial are encouraging, given its small sample size and the availability of other effective and less expensive all-oral antiviral regimens, this regimen should be considered as a second-line option until further data emerge.

Recommendation:

19. In treatment-naive patients with HCV genotype 1a or 1b infection, with or without cirrhosis, SOF (400 mg daily) and SIM (150 mg daily) should be given for 12 weeks without RBV (Class 1, Level B).

PEG-IFN-containing regimens

Given the efficacy and markedly improved tolerability of SOF or SIM combined with PEG-IFN and RBV compared with TVR- or BOC-based regimens, the latter first-generation PIs should no longer be used except in rare circumstances where treatment is urgent and access to newer agents is not available. The use of BOC and TVR is reviewed in the 2012 version of the present guidelines (3).

SOF, PEG-IFN and RBV: SOF (400 mg daily) was combined with PEG-IFN and RBV for 12 weeks in patients with HCV genotypes 1, 4, 5 and 6 in the uncontrolled, open-label, phase 3 NEUTRINO trial (5). Among patients with HCV genotype 1, the SVR12 rate was 89% (261 of 292). Although a higher proportion of patients with genotype 1a achieved SVR12 than those with genotype 1b (92% [206 of 225] versus 82% [54 of 66]), this difference was not statistically significant. In multivariate analysis, the presence of cirrhosis and a non-CC IL28B genotype were the only predictors of virological failure. The SVR12 rate was 92% (252 of 273) in noncirrhotic patients versus 80% (43 of 54) in patients with compensated cirrhosis. The SVR12 rate was 98% (93 of 95) in patients with the IL28B CC genotype, compared with 87% (202 of 232) in those with a non-CC genotype. Although the side effect profile appeared similar to that of PEG-IFN and RBV dual therapy, the uncontrolled nature of the study precluded a clear evaluation of safety. However, only 2% of patients discontinued treatment due to an adverse event. Among the 28 patients who relapsed (9% of the cohort), resistance to SOF was not detected by deep sequencing (5).

Recommendation:

20. In patients with HCV genotype 1a or 1b, with or without cirrhosis, SOF (400 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks (Class 1, Level B).

SIM, PEG-IFN and RBV: In the QUEST-1 and QUEST-2 phase 3 trials (6,7), conducted in North America and Europe, respectively, the second-generation PI SIM (150 mg once daily) was combined with PEG-IFN and weight-based RBV for 12 weeks followed by an additional 12 or 36 weeks of PEG-IFN plus RBV and compared with PEG-IFN plus RBV for 48 weeks in patients with HCV genotype 1. Patients randomly assigned to triple therapy who had HCV RNA <25 IU/mL at week 4 and undetectable HCV RNA at week 12 continued PEG-IFN plus RBV for 12 additional weeks and then stopped all treatment. Patients who did not meet these early response criteria continued PEG-IFN and RBV for an additional 36 weeks (ie, 48 weeks total). In pooled data from these trials, the SVR12 rate in the SIM/PEG-IFN/RBV groups was 80% (419 of 521), significantly higher than in

patients receiving PEG-IFN and RBV alone (50% [132 of 264]) (6,7). In total, 88% (459 of 521) of patients in the SIM/PEG-IFN/RBV groups qualified for shortened therapy and 88% (405 of 459) of these patients achieved SVR12. In the two trials, of the 12% (62 of 521) of patients who did not qualify for shortened therapy, the SVR12 rate was 32% despite up to 36 weeks of additional PEG-IFN and RBV. SVR12 rates differed according to baseline fibrosis level, decreasing from 84% (317 of 378) in patients with F0 to F2 fibrosis to 60% (29 of 48) in those with cirrhosis. The IL28B genotype was also important, with SVR12 rates of 95% (144 of 152) in CC patients treated with triple therapy compared with 80% (63 of 79) with PEG-IFN and RBV alone, and 75% (275 of 369) in patients with a non-CC genotype who received triple therapy compared with 37% (69 of 185) in the control arm.

The most important predictor of response was the presence of the Q80K polymorphism at baseline (described above). In pooled data from these trials (6,7), the SVR12 rate with SIM-based triple therapy was 58% (49 of 84) in patients with genotype 1a and Q80K; no different than that seen in the PEG-IFN and RBV control arm (52% [23 of 44]). In contrast, among patients with genotype 1a infection without Q80K, the SVR12 rate was 84% (138 of 165), similar to that seen in patients with genotype 1b infection (85% [228 of 267]) and significantly higher than found in the control arms (43% [36 of 83] in genotype 1a without Q80K and 53% [70 of 133] in genotype 1b). In these trials, the Q80K polymorphism was present at baseline in 34% of patients with genotype 1a infection and available sequencing data, but in only one of 400 patients with genotype 1b (6,7). Rates of Q80K positivity among patients with HCV genotype 1a in Canada have been reported to be as high as 47% (79).

SIM was well tolerated in these trials (6,7). In pooled data across the SIM study program (80), the main adverse events seen more frequently in SIM-treated patients were rash (mostly mild) seen in 23% of patients (versus 17% of controls) and photosensitivity in 3.3% (versus 0.5% of controls). Total bilirubin elevation, which is due to inhibition of biliary transporters and RBV-related hemolytic anemia, was observed in 7.9% of patients (versus 2.8% of controls). Notably, the incidence of anemia was similar among patients treated with SIM-based triple therapy versus PEG-IFN and RBV alone.

Recommendations:

21. In patients with HCV genotype 1b infection and patients with genotype 1a infection without the Q80K polymorphism, SIM (150 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks followed by an additional 12 weeks of PEG-IFN plus RBV (Class 1, Level A).
22. Patients with genotype 1a infection must be tested for the Q80K polymorphism before starting therapy with SIM, PEG-IFN and RBV. Patients with the Q80K polymorphism should be treated with an alternative regimen (Class 1, Level A).
23. RGT should not be used with SIM, PEG-IFN and RBV. Patients who have HCV RNA ≥25 IU/mL at week 4 or detectable HCV RNA at week 12 should stop all therapy given the low probability of SVR and the need for prolonged exposure to PEG-IFN and RBV (Class 2b, Level C).

TREATMENT-EXPERIENCED PATIENTS WITH HCV GENOTYPE 1 (TABLE 5)

PEG-IFN-free regimens

Patients who have failed IFN-based therapy should be categorized as relapsers (undetectable HCV RNA during treatment with reappearance of HCV RNA within six months of stopping therapy), partial responders (decline of at least 2 $\log_{10}$ IU/mL in HCV RNA without ever achieving undetectable HCV RNA during therapy), or null responders (<2 $\log_{10}$ IU/mL decline in HCV RNA during therapy; or breakthrough [increase by >1 $\log_{10}$ IU/mL in HCV RNA above nadir despite ongoing antiviral therapy]) (3). Patients with an unknown previous response should be managed as null responders. As in treatment-naive patients, all previously treated patients with HCV genotype 1 would benefit from all-oral DAA regimens rather than those containing IFN because these patients, with the exception of relapsers, have demonstrated poor IFN responsiveness.

SOF/LDV: The single tablet regimen of SOF/LDV was evaluated in treatment-experienced patients in the ION-2 phase 3 trial (9). The study included relapsers (56%) and nonresponders (44%), including patients who had failed PEG-IFN/RBV dual therapy (48%) or in combination with a PI (52%). Patients were randomly assigned to receive 12 or 24 weeks of treatment with or without weight-based RBV. The SVR12 rate was 94% (102 of 109) in patients who received 12 weeks of SOF/LDV and 96% (107 of 111) in those who also received RBV. The SVR12 rate in patients who received 24 weeks of SOF/LDV therapy was 99% (218 of 220 overall) whether the patients also received RBV. Virological relapse occurred in 4% to 6% of patients treated for 12 weeks, but in none treated for 24 weeks. The SVR12 rate in patients with compensated cirrhosis (20% of each treatment arm) treated for 12 weeks with SOF/LDV alone was 86% (19 of 22) versus 82% (18 of 22) in those who also received RBV. In cirrhotic patients treated for 24 weeks (with or without RBV), the SVR12 rate was 100% (44 of 44). No baseline or on-treatment predictors of relapse were identified in patients with cirrhosis. There were no differences in SVR12 rates according to receipt of RBV, previous antiviral regimen (PEG-IFN/RBV versus PEG-IFN/RBV plus a PI), or previous treatment response (relapse versus nonresponse). Among the 62 patients (14%) with detectable NS5A resistance at baseline, 55 (89%) achieved an SVR12. All 11 patients who relapsed had detectable NS5A resistance at the time of relapse, but SOF-associated resistance was not detected. Among patients previously treated with a PI-containing regimen, 71% had NS3/4A resistance at baseline and 98% of these patients achieved an SVR12 (9). Tolerability of SOF/LDV was similar to that observed in the ION-1 and ION-3 studies (see above) (8,10); more adverse events were reported in patients treated with RBV.

Based on the higher rates of response observed in the ION-2 trial among previous treatment failure patients with compensated cirrhosis treated for 24 versus 12 weeks, Health Canada and the FDA have recommended a 24-week regimen of SOF/LDV in this patient subgroup. However, a subsequent and significantly larger randomized trial from France (the SIRIUS trial) (81) suggested that a 12-week regimen of SOF/LDV plus weight-based RBV is as effective as a 24-week SOF/LDV regimen in patients with cirrhosis who had failed both PEG-IFN/RBV and triple therapy including a PI. Specifically, 74 of 77 patients (96%) randomly assigned to SOF/LDV/RBV for 12 weeks had an SVR12 (4% relapse rate) compared with 75 of 77 patients (97%) randomly assigned to SOF/LDV alone for 24 weeks (3% relapse rate). Furthermore, in a pooled analysis of data from the SIRIUS trial and six other phase 2 and 3 studies that included 352 treatment-experienced patients with cirrhosis (82), 12 weeks of SOF/LDV/RBV resulted in a similar SVR12 rate to 24 weeks of SOF/LDV alone (96% versus 98%).

Recommendations:

24. In noncirrhotic patients with HCV genotype 1 who have failed previous therapy with PEG-IFN and RBV, with or without a PI, SOF/LDV without RBV should be given for 12 weeks (Class 1, Level B).
25. In cirrhotic patients with genotype 1 who have failed previous therapy with PEG-IFN and RBV, with or without a PI, SOF/LDV and weight-based RBV should be given for 12 weeks (Class 1, Level A).

PTV_R/OBV/DSV and RBV: The combination of PTV_R/OBV/DSV with weight-based RBV was evaluated in treatment-experienced patients without cirrhosis in the SAPPHIRE-II phase 3 trial (14). Among 297 patients randomly assigned to PTV_R/OBV/DSV plus RBV regimen for 12 weeks, 286 (96%) achieved SVR12. No pre- or on-treatment predictors of response were identified. The SVR12 rate was

TABLE 5
Treatment-experienced patients with hepatitis C virus (HCV) genotype 1

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 1a, noncirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks†	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24–48 weeks (if Q80K–)†‡	PEG/RBV/BOC or TVR
				SIM/PEG/RBV (if Q80K+)
Genotype 1b, noncirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks†	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV × 12 weeks		SIM/PEG/RBV × 24–48 weeks†,‡	PEG/RBV/BOC or TVR
Genotype 1a, cirrhotic	SOF/LDV/RBV × 12 weeks	SOF/LDV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12–24 weeks*	SOF/SIM × 12 weeks†	SIM/PEG/RBV × 24–48 weeks (if Q80K–)†‡	PEG/RBV/BOC or TVR
				SIM/PEG/RBV if Q80K+)
Genotype 1b, cirrhotic	SOF/LDV/RBV × 12 weeks	SOF/LDV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks	SOF/SIM × 12 weeks†	SIM/PEG/RBV × 24–48 weeks†‡	PEG/RBV/BOC or TVR

**Patients with HCV genotype 1a, cirrhosis and previous null response should receive 24 weeks of PTV_R/OBV/DSV/RBV (paritaprevir//ritonavir/ombitasvir/dasabuvir/ribavirin) if treated with this regimen. Relapsers and partial responders with genotype 1 and cirrhosis can be treated for 12 weeks with PTV_R/OBV/DSV/RBV; †Simeprevir (SIM)-containing regimens should not be given to patients who have failed previous therapy with a protease inhibitor; ‡Previous null responders with genotype 1a or 1b should not be treated with SIM/ Peginterferon alfa-2a or peginterferon alfa-2b (PEG)/RBV regardless of the presence or absence of cirrhosis. Previous relapsers should be treated for 24 weeks total (12 weeks of SIM/PEG/RBV followed by 12 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at week 12. Otherwise, all treatment should be discontinued. Partial responders should be treated for 48 weeks total (12 weeks of SIM/PEG/RBV followed by 36 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at weeks 12 and 24; otherwise, all treatment should be discontinued. + Positive; – Negative; BOC Boceprevir; DSV: 250 mg one tablet twice daily; IFN Interferon; PEG: Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV: 150 mg/100 mg/25 mg, two tablets once daily; Q80K SIM-associated resistance variant at position 80; RBV weight-based dosing: 1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg; SIM: 150 mg once daily; SOF Sofosbuvir (400 mg once daily); SOF/LDV SOF 400 mg/ledipasvir 90 mg once daily (one tablet); TVR Telaprevir*

similar between patients with genotype 1a (96% [166 of 173]) and 1b (97% [119 of 123]), and did not differ between relapsers (95% [82 of 86]), partial responders (100% [65 of 65]) and null responders (95% [139 of 146]). RAVs to one or more of the three DAAs in the regimen were detected in five of the seven patients with post-treatment relapse (14).

In the TURQUOISE-II trial (13), PTV_R/OBV/DSV plus RBV regimen for 12 or 24 weeks was evaluated in 380 patients with compensated cirrhosis, of whom 58% had previously failed PEG-IFN and RBV therapy. Among patients with genotype 1b, the SVR12 rate was 99% (67 of 68) with 12 weeks of therapy and 100% (51 of 51) with 24 weeks. Response rates did not differ according to treatment duration or previous treatment history. In patients with genotype 1a infection, SVR12 rates were 89% (124 of 140) with 12 weeks and 94% (114 of 121) with 24 weeks of therapy; this difference was not statistically significant. There was no difference between the 12- and 24-week study arms among treatment-naive, cirrhotic patients with genotype 1a (12 versus 24 weeks: 92% [59 of 64] versus 93% [52 of 56]), previous relapsers (93% [14 of 15] versus 100% [13 of 13]) or partial responders (100% [11 of 11] versus 100% [10 of 10]). However, among null responders with genotype 1a, the 24-week arm was superior to 12 weeks of treatment (93% [39 of 42] versus 80% [40 of 50]) (13).

To determine the importance of RBV in noncirrhotic, treatment-experienced patients with HCV genotype 1b infection, the PEARL-II study randomly assigned patients to receive PTV_R/OBV/DSV with or without RBV for 12 weeks (83). All 91 patients (100%) who received PTV_R/OBV/DSV alone achieved SVR12 compared with 97% (85 of 88) randomly assigned to also receive RBV.

There is expected to be overlap between RAVs due to PI-based therapies. Because the PTV_R/OBV/DSV regimen contains a PI and other regimens with documented activity in these patients are available (ie, SOF/LDV) (9), this regimen should not be used in patients who have failed another PI (eg, TVR, BOC or SIM).

Recommendations:

26. In noncirrhotic, treatment-experienced patients with HCV genotype 1a infection, coformulated PTV_R/OBV/DSV should be given with weight-based RBV for 12 weeks (Class 1, Level A).
27. In noncirrhotic, treatment-experienced patients with genotype 1b infection, coformulated PTV_R/OBV/DSV should be given without RBV for 12 weeks (Class 1, Level A).
28. In cirrhotic patients with genotype 1a infection and a history of previous null response to PEG-IFN and RBV, coformulated PTV_R/OBV/DSV should be given with RBV for 24 weeks (Class 1, Level B).
29. In patients who have failed therapy with another PI, coformulated PTV_R/OBV/DSV should not be given due to the potential for cross-resistance with PTV (Class 2b, Level C).

SOF and SIM: As previously described, SOF (400 mg daily) was combined with the PI SIM (150 mg daily) with or without RBV for 12 or 24 weeks in the phase 2 COSMOS study (76). Cohort 1 included 80 null responders with mild fibrosis (F0 to F2) and cohort 2 included 47 null responders (plus 40 treatment-naive patients) with advanced fibrosis (F3 and F4). Overall, 116 of 127 null responders (91%) achieved an SVR12, not significantly different from that observed among treatment-naive subjects (95% [38 of 40]). SVR12 rates among null responders were similar regardless of fibrosis severity (F0 to F2: 90% [72 of 80] versus F3: 96% [23 of 24] versus F4: 91% [21 of 23]), treatment duration or receipt of RBV. Given the expected cross-resistance between other PIs and SIM, patients who previously failed treatment with these agents were excluded from the study (76). Because of the small sample size of this trial and the availability of other effective and less expensive IFN-free regimens, this combination should be considered as a second line option until further data emerge.

Recommendations:

30. In patients with HCV genotype 1a or 1b infection, with or without cirrhosis, who have failed previous therapy with PEG-IFN and RBV, SOF (400 mg daily) and SIM (150 mg daily) should be given without RBV for 12 weeks (Class 1, Level B).
31. The combination of SOF and SIM should not be used in patients who have failed therapy with another PI (Class 2b, Level C).

PEG-IFN-containing regimens

Given the efficacy and markedly improved safety and tolerability of SOF and SIM combined with PEG-IFN and RBV compared to TVR or BOC-based regimens, these first generation PIs should no longer be used except in rare circumstances (see above).

SOF, PEG-IFN and RBV: Experience with the use of SOF (400 mg) in combination with PEG-IFN and RBV in patients who have failed IFN-based therapy is limited. Nevertheless, Health Canada and the United States FDA have approved this regimen for treatment-experienced patients. Based on a modelling approach, the FDA projected an SVR12 rate of 78% in PEG-IFN and RBV treatment failures if retreated with SOF plus PEG-IFN/RBV for 12 weeks. In the NEUTRINO phase 3 trial of treatment-naive patients (5), 52 patients with HCV genotype 1 had characteristics typical of the treatment-experienced population (ie, advanced fibrosis [F3 and F4], a non-CC IL28B genotype and high baseline viral load [≥800,000 IU/mL]). Thirty-seven of these patients (71%) achieved SVR12 with 12 weeks of SOF/PEG-IFN/RBV (74). Although this regimen is also untested in patients who have failed therapy with a PI, the absence of cross-resistance between the PIs and SOF suggests that these patients should respond similarly to those who failed treatment with PEG-IFN/RBV alone.

Recommendation:

32. In patients with HCV genotype 1a or 1b infection, with or without cirrhosis, who have failed previous therapy with PEG-IFN and RBV with or without a PI, SOF (400 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks (Class 2b, Level C).

SIM, PEG-IFN and RBV: SIM (150 mg daily) has been evaluated in combination with PEG-IFN and weight-based RBV for 12 weeks followed by an additional 12 to 36 weeks of PEG-IFN and RBV in patients with HCV genotype 1 who failed IFN-based therapy in two trials. The phase 3 PROMISE study (84) included relapsers, whereas the phase 2b ASPIRE trial (85) also included partial and null responders. In the PROMISE trial (84), an RGT approach identical to that used in treatment-naive patients was evaluated (see above). Treatment with triple therapy was more effective than PEG-IFN and RBV dual therapy (SVR12: 79% [206 of 260] versus 36% [48 of 133]) in these relapsers. The majority of SIM-treated patients (93% [241 of 260]) were eligible to shorten treatment from 48 to 24 weeks and 83% of these patients (200 of 241) achieved SVR12. In patients with undetectable HCV RNA at week 4 (77% of the cohort), the SVR12 rate was 87% (173/200), compared with 60% in those with HCV RNA <25 IU/mL but detectable at week 4. Among patients who did not qualify for shortened therapy, the SVR12 rate was 40% (six of 15) despite 48 weeks of treatment. Of the 39 patients with compensated cirrhosis randomly assigned to triple therapy, 29 (74%) achieved SVR12 compared with five of 19 (26%) in the control arm. As reported in treatment-naive subjects from the QUEST-1 and QUEST-2 trials (6,7), patients with HCV genotype 1a and the Q80K mutation at baseline did not benefit from SIM treatment (SVR12 rates in the simeprevir and placebo arms: 47% [14 of 30] versus 30% [six of 20], respectively). RAVs similar to those selected by TVR and BOC emerged in most patients (90%) who did not achieve SVR12 in the SIM arm (84).

In the phase 2b ASPIRE trial (85), 462 patients who failed PEG-IFN/RBV therapy (40% relapsers, 35% partial responders and 25% null responders) were randomly assigned to receive SIM (100 mg or 150 mg or placebo) for 12, 24 or 48 weeks in combination with PEG-IFN and RBV for 48 weeks. In patients treated with SIM 150 mg daily for 12 weeks, SVR24 rates were 77% (20 of 26) in relapsers, 65% (15 of 23) in partial responders and 44% (eight of 18) in null responders; all superior to rates in the control arm (37%, 19% and 9%, respectively). Among null responders with cirrhosis (across all SIM 150 mg arms), 31% (four of 13) achieved SVR24 with SIM compared with neither of two patients treated with PEG-IFN and RBV.

Recommendations:

33. In patients with HCV genotype 1b or genotype 1a infection without the Q80K polymorphism who relapsed to PEG-IFN and RBV, SIM (150 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks followed by PEG-IFN plus RBV for an additional 12 weeks. All therapy should be discontinued in patients who have HCV RNA >25 IU/mL at week 4 or detectable HCV RNA at week 12 (Class 1, Level A).
34. In patients with previous partial or null response, alternative regimens should be considered given the low probability of SVR and the need for prolonged exposure to PEG-IFN and RBV with this regimen (Class 2b, Level B).

PATIENTS WITH HCV GENOTYPE 2 (TABLE 6)

SOF and RBV

In the phase 3 FISSION trial (5), SOF (400 mg daily) was administered in combination with weight-based RBV for 12 weeks to treatment-naive patients with HCV genotype 2. Patients randomly assigned to the control arm received a 24-week course of PEG-IFN and RBV (800 mg daily). Patients with cirrhosis accounted for approximately 20% of the study population. The SVR12 rates in the SOF/RBV and PEG-IFN/RBV arms were 97% (68 of 70) and 78% (52 of 67), respectively. The incidence of adverse events was consistently lower among patients who received SOF/RBV, particularly the influenza-like symptoms and depression characteristic of IFN-based therapy. In the phase 3 VALENCE trial (12), 32 treatment-naive patients with HCV genotype 2 received a 12-week regimen of SOF and weight-based RBV. As observed in the FISSION study (5), all but one of these patients (97%) achieved an SVR12. The response rate did not differ between cirrhotic (100% [two of two]) and noncirrhotic patients (97% [29 of 30]). In the phase 3 POSITRON trial (11), 143 IFN-ineligible patients with HCV genotype 2 were randomly assigned to receive SOF and weight-based RBV for 12 weeks or placebo. The majority of patients in this trial had contraindications to or refused IFN therapy; only 7% had previously

TABLE 6
Patients with hepatitis C virus genotype 2

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Treatment-naive	SOF/RBV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
			PEG/RBV × 24 weeks*	SOF/LDV
				PTV_R/OBV/DSV ± RBV
				SOF/SIM
Treatment-experienced, noncirrhotic	SOF/RBV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	PEG/RBV
Treatment-experienced, cirrhotic	SOF/PEG/RBV × 12 weeks	SOF/RBV × 16 weeks*	None	PEG/RBV/PI
				SOF/LDV
				PTV_R/OBV/DSV ± RBV
				SOF/SIM

**Clinically inferior regimen. DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PI Protease inhibitor (eg, boceprevir, telaprevir or simeprevir); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV Ribavirin (weight-based dosing [1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg] if combined with sofosbuvir (SOF); 800 mg daily if used in dual therapy with PEG); SIM Simeprevir (150 mg daily); SOF: 400 mg daily; SOF/LDV SOF 400 mg/ledipasvir 90 mg once daily (one tablet)*

failed IFN-based treatment. Among 109 patients with genotype 2 treated with SOF/RBV for 12 weeks, 101 patients (93%) achieved an SVR12, similar to results observed in the FISSION and VALENCE trials (5,12). SVR12 rates did not differ between patients with and without cirrhosis (94% [16 of 17] versus 92% [85 of 92]).

SOF (400 mg daily) and weight-based RBV has also been studied in treatment-experienced patients with HCV genotype 2 in the VALENCE (12) and FUSION (11) phase 3 trials. In VALENCE (12), 37 of 41 (90%) treatment-experienced patients had an SVR12 following a 12-week course of SOF/RBV. In the FUSION trial (11), 68 patients who had previously failed an IFN-containing regimen (approximately 75% due to relapse), were randomly assigned to receive SOF/RBV for either 12 or 16 weeks. Overall, an SVR12 was observed in 86% (31 of 36) of patients treated for 12 weeks versus 94% (30 of 32) treated for 16 weeks, although this difference was not statistically significant. In patients without cirrhosis, high rates of SVR12 were observed regardless of treatment duration (12 versus 16 weeks: 96% [25 of 26] versus 100% [23 of 23]). However, lower rates of response were observed among patients with cirrhosis (12 versus 16 weeks: 60% [six of 10] versus 78% [seven of nine]). Although this difference was not statistically significant, the poor response rate among patients treated for 12 weeks suggests that a 16-week regimen is preferred if SOF/RBV is prescribed to this patient subgroup, particularly in IFN-ineligible subjects. Tolerability of SOF/RBV was similar to that observed in the FISSION and POSITRON studies (5,11).

SOF, PEG-IFN and RBV

SOF, PEG-IFN, and weight-based RBV for 12 weeks has been studied in patients with HCV genotype 2 who failed previous therapy in an open-label phase 2 study (86). Among 23 patients with HCV genotype 2 (14 with cirrhosis), an SVR12 rate of 96% (22 of 23) was observed. High rates of response were observed among cirrhotic (93% [13 of 14]) and noncirrhotic patients (100% [nine of nine]). Among the entire study population (n=47), which also included 24 patients with genotype 3, three patients discontinued RBV due to anemia and one patient discontinued all therapy due to pain. Serious adverse events occurred in four patients (9%); the majority were considered due to PEG-IFN or RBV and none due to SOF.

Recommendations:

35. In treatment-naive patients with HCV genotype 2, SOF (400 mg daily) should be given with weight-based RBV for 12 weeks (Class 1, Level A).
36. In noncirrhotic, treatment-experienced patients with genotype 2, SOF (400 mg daily) should be given with weight-based RBV for 12 weeks (Class 1, Level A).
37. In IFN-eligible, treatment-experienced patients with genotype 2 and cirrhosis, SOF (400 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks. In IFN-ineligible patients, SOF (400 mg daily) should be given with weight-based RBV for 16 weeks (Class 1, Level B).

PATIENTS WITH HCV GENOTYPE 3 (TABLE 7)

SOF and RBV

In the phase 3 FISSION trial (5), SOF (400 mg daily) in combination with weight-based RBV for 12 weeks or PEG-IFN/RBV (800 mg daily) for 24 weeks were administered to 359 treatment-naive patients with HCV genotype 3. Overall, an SVR12 was observed in 56% (102 of 183) of patients randomly assigned to receive SOF/RBV compared with 63% (110 of 176) in those treated with PEG-IFN/RBV. This difference was not statistically significant. In light of the suboptimal responses observed with a 12-week SOF/RBV regimen in this trial, the VALENCE trial examined a 24-week course in patients with HCV genotype 3 (12). Among treatment-naive patients, 94% (99 of 105) achieved an SVR12; responses did not differ between cirrhotic (92% [12 of 13]) and noncirrhotic patients (95% [87 of 92]).

SOF/RBV combination therapy has also been studied in treatment-experienced patients with HCV genotype 3. In the FUSION phase 3 trial (11), 127 patients who had failed previous treatment were randomly assigned to 12 or 16 weeks of SOF and weight-based RBV. Overall, SVR12 rates were 30% (19 of 64) and 62% (39 of 63) in the 12- and 16-week groups, respectively. The presence of cirrhosis was a strong negative predictor of response in patients treated for 12 weeks; only 19% (five of 26) of cirrhotic patients and 37% (14 of 38) of noncirrhotic patients had an SVR12 with this regimen. In the 16-week treatment arm, SVR12 rates were 61% (14 of 23) among patients with cirrhosis and 63% (25 of 40) in those without cirrhosis. In this trial, the primary mode of treatment failure was relapse, which was observed among 66% (42 of 64) of patients treated for 12 weeks and 38% (24 of 63) of those treated for 16 weeks. Therefore, the VALENCE trial examined a longer course (24 weeks) of SOF/RBV therapy in 145 treatment-experienced patients with HCV genotype 3 (12). Among 98 noncirrhotic patients in this trial, an SVR12 was observed in 85 (87%). However, only 62% (29 of 47) of patients with cirrhosis had an SVR12. Based on these data, alternative treatment options are necessary in cirrhotic, treatment-experienced patients with HCV genotype 3.

SOF, PEG-IFN and RBV

SOF, PEG-IFN and weight-based RBV administered for 12 weeks was studied in patients with HCV genotype 3 who failed previous therapy in a small, open-label phase 2 study (86). Among 24 patients, 12 of whom had cirrhosis, an SVR12 rate of 83% (20 of 24) was observed. There was no difference in response between cirrhotic and noncirrhotic patients (83% [10 of 12] in both groups).

SOF/LDV plus RBV

The single tablet regimen of SOF/LDV has been studied in patients with HCV genotype 3 in the open-label, phase 2, ELECTRON-2 trial conducted in two centres in New Zealand (87). In this study, 51 treatment-naive patients (16% with cirrhosis) were randomly assigned to 12 weeks of SOF/LDV with or without weight-based RBV. Fifty treatment-experienced patients (44% with cirrhosis) all received SOF/LDV plus RBV. Among treatment-naive patients, SVR12 rates were 64% (16 of 25) in the SOF/LDV group and 100% (26 of 26) in those who received SOF/LDV plus RBV. In treatment-experienced patients

TABLE 7
Patients with hepatitis C virus genotype 3

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Treatment-naive, noncirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
			PEG/RBV × 24 weeks*	PTV_R/OBV/DSV ± RBV
				SOF/SIM
Treatment-naive, cirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
Treatment-experienced, noncirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
Treatment-experienced, cirrhotic	SOF/PEG/RBV × 12 weeks	SOF/RBV × 24 weeks*	None	PTV_R/OBV/DSV ± RBV
		SOF/LDV/RBV × 12 weeks		SOF/SIM

**Approved, but clinically inferior regimen. DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PI Protease inhibitor (eg, boceprevir, telaprevir or simeprevir); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV Ribavirin (weight-based dosing [1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg] if combined with sofosbuvir (SOF); 800 mg daily if used in dual therapy with PEG); SIM Simeprevir (150 mg daily); SOF: 400 mg daily; SOF/LDV SOF (400 mg)/ledipasvir (90 mg) once daily (one tablet)*

treated with SOF/LDV/RBV for 12 weeks, noncirrhotic patients had higher SVR12 rates than those with cirrhosis (89% [25 of 28] versus 73% [16 of 22]). LDV has limited activity against genotype 3 HCV in vitro (88); therefore, although SOF/LDV is a potential therapeutic option in these patients, additional data in diverse populations are necessary before it can be recommended as first-line therapy over other SOF-containing regimens.

Recommendations:

38. In treatment-naive patients and noncirrhotic treatment-experienced patients with HCV genotype 3, SOF (400 mg daily) should be given with weight-based RBV for 24 weeks (Class 1, Level B).
39. In cirrhotic, treatment-experienced patients with HCV genotype 3, SOF (400 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks (Class 1, Level B).

PATIENTS WITH HCV GENOTYPES 4, 5 AND 6 (TABLE 8)

There are limited data to guide treatment decision-making for patients with HCV genotypes 4, 5 or 6 due to the small numbers of patients enrolled in phase 3 clinical trials. In Canada, these genotypes are present in <1% of cases (22). Although the first-generation PIs, BOC and TVR, do not have clinically significant activity against genotypes 4, 5 or 6, SOF (5) and SIM (89) have activity against all of these genotypes. However, due to a paucity of published data, Health Canada and the United States FDA have approved only SOF for the treatment of HCV genotype 4.

PEG-IFN-free regimens

PTV_R/OBV ± RBV: The fixed-dose combination of the ritonavir-boosted, NS3/4A PI PTV_R and the NS5A inhibitor OBV was studied in patients with HCV genotype 4 in the PEARL-I study (90). Treatment-naive patients were randomly assigned to receive PTV_R/OBV with or without weight-based RBV for 12 weeks; all treatment-experienced patients received RBV. Nearly all patients (93%) in this study had mild fibrosis (F0 to F2) and none had cirrhosis. Among subjects who received PTV_R/OBV plus RBV, all treatment-naive (42 of 42) and treatment-experienced patients (41 of 41) achieved an SVR12. However, the SVR12 rate was lower (91% [40 of 44]) among treatment-naive patients randomly assigned to the RBV-free regimen, suggesting that RBV is necessary with this drug combination. The safety profile of PTV_R/OBV plus RBV was similar to that observed in patients with HCV genotype 1 who were also treated with DSV (14,15).

SOF/LDV: The single tablet regimen of SOF/LDV was evaluated in patients with HCV genotype 4 in a single-center, open-label phase 2a trial (National Institutes of Allergy and Infectious Diseases SYNERGY) (91). Twenty-one patients (38% treatment-experienced; 40% with cirrhosis) received SOF/LDV for 12 weeks. Among 20 patients who completed the post-treatment follow-up period, 19 (95%) achieved SVR12. No patient discontinued treatment due to an adverse event. In a similar, open-label study conducted among 25 patients with HCV genotype 6 (92% treatment-naive; 8% with cirrhosis; 80% IL28B CC genotype) from two centres (ELECTRON-2) (87), a 12-week regimen of SOF/LDV resulted in an SVR12 rate of 96% (24 of 25). Although in vitro data suggest that SOF/LDV should be efficacious in patients with HCV genotype 5 (88), it cannot currently be recommended in this patient subgroup until clinical trial data are available.

SOF and RBV: The all-oral combination of SOF (400 mg daily) and weight-based RBV for 12 or 24 weeks was studied in a randomized trial conducted among 103 Egyptian patients with HCV genotype 4 (52% treatment-experienced; 17% with compensated cirrhosis) (92). Among treatment-naive subjects, the SVR12 rates in the 12- and 24-week treatment arms were similar (84% [21 of 25] versus 92% [22 of 24]). Whereas noncirrhotic patients had similar responses in the 12- and 24-week treatment arms (86% [19 of 22] versus 90% [19 of 21]), patients with cirrhosis appeared to benefit from prolonged therapy (SVR12 in 12- versus 24-week arms: 67% [two of three] versus 100% [three of three]); however, the sample size was limited. Among treatment-experienced patients (41% nonresponders), a 24-week regimen was superior overall (SVR12 rates in 12- versus 24-week arms: 70% [19 of 27] versus 89% [24 of 27]) and in noncirrhotic patients (73% [16 of 22] versus 95% [20 of 21]). In patients with cirrhosis, SVR12 rates in the 12- and 24-week treatment groups were 60% (three of five) and 67% (four of six), respectively (92). These results were supported by a small trial of Egyptian persons living in the United States treated with SOF and weight-based RBV for 12 or 24 weeks (93). In treatment-naive patients, the SVR12 rate was 79% (11 of 14) in patients treated for 12 weeks and 100% (14 of 14) in those treated for 24 weeks. In treatment-experienced patients, corresponding SVR12 rates were 59% (10 of 17) and 87% (13 of 15).

PEG-IFN-containing regimens

SOF, PEG-IFN and RBV: In the phase 2 ATOMIC study (94), SOF (400 mg once daily) was administered for 24 weeks in combination with PEG-IFN/RBV to a small number of patients with HCV genotypes 4 and 6. SVR12 rates of 82% (nine of 11) in patients with genotype 4 and 100% (five of five) in genotype 6 were observed, supporting the antiviral activity of this regimen. In the phase 3 NEUTRINO study (5), a small subset of patients with HCV genotypes 4 (n=28), 5 (n=1) and 6 (n=5) received this regimen for a shorter 12-week treatment period, and SVR12 rates of 96% (27 of 28) in patients with genotype 4 and 100% (six of six) for genotypes 5 and 6 were reported. The one patient with genotype 4 who failed to achieve an SVR12 had cirrhosis and relapsed after cessation of therapy. The tolerability was similar to that observed historically among patients treated with PEG-IFN and RBV.

SIM, PEG-IFN and RBV: The RESTORE study was a phase 3, single-arm, open-label trial that evaluated SIM with PEG-IFN/RBV in 35 treatment-naive and 72 treatment-experienced patients with HCV genotype 4 (95). All patients received 12 weeks of triple therapy followed by 12 or 36 weeks of PEG-IFN and RBV dual therapy. Treatment-naive and relapser patients were eligible for RGT (an additional 12 weeks of PEG-IFN and RBV dual therapy if HCV RNA <25 IU/mL at week 4 and undetectable at week 12; otherwise, an additional 36 weeks) while partial and null responders received 36 weeks of dual therapy (48 weeks total). Overall, 65% (70 of 107) of patients achieved SVR12 (83% [29 of 35] of treatment-naive patients, 86% [19 of 22] of relapsers, 60% [six of 10] of partial responders and 40% [16 of 40] of null responders). The majority of patients (89% of treatment-naive and 91% of relapsers) met criteria for shortened therapy and SVR12 rates of 94% and 95% were observed in these groups, respectively. Safety was similar to that observed in other phase 3 trials of SIM/PEG-IFN/RBV therapy (6,7).

Recommendations:

40. Patients with HCV genotype 4 should be treated with coformulated PTV_R/OBV plus weight-based RBV or SOF/LDV alone for 12 weeks (Class 1, Level B).
41. Patients with HCV genotype 5 should be treated with SOF (400 mg daily) and PEG-IFN plus weight-based RBV for 12 weeks (Class 1, Level B).
42. Patients with HCV genotype 6 should be treated with SOF/LDV for 12 weeks (Class 1, Level B).

ANTIVIRAL RESISTANCE

Emergence of RAVs must be considered with all DAA-based therapies. Due to the high replication rate of HCV and the low fidelity of its RNA-dependent RNA polymerase, new variants emerge continuously (96-98). HCV circulates as a large of population of related viruses known as quasispecies. Variants with mutations that lead to DAA resistance emerge by chance and are present at low frequencies

TABLE 8
Patients with hepatitis C virus (HCV) genotypes 4, 5 and 6

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 4	PTV_R/OBV/RBV × 12 weeks	SOF/RBV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	SOF/LDV × 12 weeks		SIM/PEG/RBV × 24-48 weeks*	PEG/RBV/BOC or TVR
Genotype 5	SOF/PEG/RBV × 12 weeks	None	None	PTV_R/OBV/DSV ± RBV
Genotype 6	SOF/LDV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	

**Treatment-naive and previous relapser patients with HCV genotype 4 should be treated for 24 weeks total (12 weeks of simeprevir/ peginterferon alfa-2a or peginterferon alfa-2b/ribavirin [SIM/PEG/RBV] followed by 12 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at week 12. Otherwise, all treatment should be discontinued. Partial and null responders with HCV genotype 4 should be treated for 48 weeks total (12 weeks of SIM/PEG/RBV followed by 36 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at weeks 12 and 24; otherwise, all treatment should be discontinued. BOC Boceprevir; DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV: weight-based dosing (1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg); SIM: 150 mg once daily; SOF Sofosbuvir (400 mg once daily); SOF/LDV SOF(400 mg)/ledipasvir (90 mg) once daily (one tablet); TVR telaprevir*

before DAA exposure. With DAA exposure, these resistant variants have a selective advantage over wild-type virus and will emerge as the dominant strains in the quasispecies. The probability that resistance will emerge with particular DAAs depends on their genetic barrier to resistance. This barrier usually reflects the number of nucleotide substitutions that must occur for high-level resistance to emerge. For example, the common PI mutation, R155K, requires two substitutions in a genotype 1b virus, but a single substitution in a genotype 1a virus and, consequently, this variant is much more common in patients with genotype 1a (99). In addition to the genetic barrier, the fitness of the RAV is important. A RAV that replicates very poorly is unlikely to emerge on therapy and will be quickly suppressed by wild-type virus once selective drug pressure is removed (97,98). For example, the S282T variant that confers resistance to SOF has extremely low replicative fitness and, as a result, has been identified only rarely in patients during SOF therapy and quickly disappears on treatment cessation (100). In contrast, many variants resistant to NS5A inhibitors are very fit and compete well with wild-type virus (88,101). As a result, NS5A-resistant variants are found in 10% to 15% of genotype 1 patients before drug exposure and persist long after therapy is discontinued in patients who fail an NS5A inhibitor-containing regimen (8,9).

Strategies to overcome resistance include avoiding DAA monotherapy and DAA dose reductions, maximizing adherence, combining DAAs with nonoverlapping resistance profiles, choosing DAAs with high barriers to resistance, and combining DAAs with PEG-IFN and RBV (96). NS5A inhibitors (eg, LDV, OBV), non-nucleoside polymerase inhibitors (eg, DSV) and NS3/4A PIs (eg, TVR, BOC, SIM) have low barriers to resistance (88). However, when potent agents of multiple classes are combined, on-treatment virological failure is extremely rare (eg, one patient of 473 treated with PTV_R/OBV/DSV plus RBV in the SAPPHIRE-I trial) and post-treatment relapse is very uncommon (eg, seven of 463 patients in this trial) (15). However, resistance to two or all three classes of drugs has been identified in almost all patients with virological failure on this combination. LDV-resistant variants are also uncommon, but present at the time of relapse in most patients who fail SOF/LDV combination therapy (8,9).

There are no data to support pretreatment resistance testing. In patients who have failed a DAA-containing regimen, it is reasonable to assume that resistance to that DAA is present at the time of retreatment. Therefore, a regimen containing DAAs without overlapping resistance should be selected in this situation. For example, in patients who have failed TVR or BOC, SOF/LDV combination therapy is very effective. In the ION-2 trial (9), 159 of 163 patients (98%) with persistent PI resistance at treatment initiation achieved an SVR12 with this regimen. Although RAVs may return to pretreatment levels after prolonged duration off therapy, there are no data on treating patients with PI resistance with a PI-containing regimen (eg, PTV_R/OBV/DSV). Therefore, this approach should not be adopted, particularly given the presence of other proven alternatives (ie, SOF/LDV).

NS5A resistance is of slightly more concern because NS5A inhibitors are a component of most all-oral regimens (88). In patients with baseline NS5A resistance, 90% achieved SVR12 with SOF/LDV in the ION-1 (8) and ION-3 (10) trials. Although this SVR rate was slightly lower than in patients without baseline resistance, the differences were not statistically significant and, therefore, pretreatment identification of resistance would not change management. Detailed baseline sequencing was not performed on all patients treated with the PTV_R/OBV/DSV regimen in the phase 3 trials (13-15,75,83); however, the rates of virological failure were low, suggesting that baseline NS5A resistance is unlikely to be a major issue. Whether retreatment of patients with emergent NS5A resistance with an NS5A-inhibitor-containing regimen will be effective remains to be determined.

Recommendations:

43. DAAs should not be used as monotherapy (Class 1, Level B).
44. Dosage reductions of DAAs should not be used to manage treatment-related side effects (Class 2a, Level C).
45. Adherence with DAAs should be maximized to reduce the likelihood of resistance (Class 2a, Level C).
46. Patients who failed therapy with a PI in the past should be treated with a regimen that does not contain a PI (Class 1, Level B).
47. With the exception of testing for Q80K in patients being considered for treatment with SIM, PEG-IFN and RBV, there is no role for baseline resistance testing with current DAA regimens (Class 1, Level A).

DDIs

Before the initiation of any DAA, potential DDIs must be considered, including those attributable to prescription and over-the-counter pharmaceuticals and herbal preparations. Identification of potential interactions requires knowledge of the metabolism of these agents. All currently available HCV PIs (TVR, BOC, SIM, PTV) are inhibitors and substrates of Cytochrome P450 3A4 (CYP3A4). Ritonavir, which is used to increase exposure and allow for once-daily dosing of PTV, is also an inhibitor and substrate of CYP3A4. Therefore, PIs are contraindicated with medications that are potent inducers of CYP3A4/5, which would reduce plasma concentrations and the therapeutic effect of the PI, and for those highly dependent on CYP3A4/5 for clearance, in which elevated plasma concentrations are associated with serious and/or life-threatening events (ie, a narrow therapeutic index). Other drug-metabolizing pathways are involved in individual PI handling that may affect DDIs. NS5A inhibitors and nucleotide polymerase inhibitors have fewer known DDIs than PIs; however, before starting therapy, all concomitant medications should be reviewed. Reference to an online updated database of DDIs is recommended before starting therapy (eg, http://www.hep-druginteractions.org).

Recommendation:

48. All prescription, over-the-counter and herbal medications should be reviewed for possible interactions with DAAs before starting therapy (Class 1, Level C).

FUTURE THERAPEUTIC OPTIONS

Numerous additional antiviral agents are under investigation in various stages of clinical development, from phase 1 though premarketing approval. Promising DAAs include NS3/4A PIs (eg, asunaprevir, grazoprevir, sovaprevir, vedroprevir), NS5A inhibitors (eg, daclatasvir, GS-5816, elbasvir, ACH-3102 and samatasvir), and non-nucleoside (eg, beclabuvir and GS-9669) and nucleotide NS5B polymerase inhibitors (eg, MK-3682 and ACH-3422). As new data regarding these agents emerge, including their receipt of regulatory approval, these HCV management guidelines will be updated.

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THE ATTACHED IS EXHIBIT "E" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 13TH DAY OF OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

Product Monograph

PrHARVONI®

(ledipasvir/sofosbuvir) tablets

90 mg/400 mg

Antiviral Agent

Gilead Sciences Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3
Canada

www.gilead.ca

Date of Preparation: 23 May 2017

Submission Control No.: 199607

TABLE OF CONTENTS

HARVONI
ledipasvir/sofosbuvir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 90 mg ledipasvir/400 mg sofosbuvir	lactose monohydrate

*For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

HARVONI (ledipasvir/sofosbuvir) is indicated for the treatment of chronic hepatitis C virus (CHC) infection in adults (≥ 18 years of age).

HARVONI is indicated for the treatment of CHC genotype 1 infection in pediatric patients ≥ 12 years of age, without cirrhosis or with compensated cirrhosis.

Geriatrics (≥ 65 years of age)

Clinical studies of HARVONI included 200 patients (8.7% of total number of patients in clinical trials) aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment groups. HARVONI can be administered in geriatric patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (< 18 years of age)

Safety and efficacy with HARVONI have been established in pediatric patients ≥ 12 years of age with genotype 1 CHC (see **CLINICAL TRIALS**).

Safety and efficacy in pediatric patients infected with other CHC genotypes or in patients who are < 12 years of age have not been established (see **WARNINGS AND PRECAUTIONS**).

Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis:

Efficacy with HARVONI + ribavirin (RBV) regimen has been established in adult CHC genotype 1 or 4 liver transplant recipients without cirrhosis, with compensated cirrhosis (CPT A) and genotype 1 liver transplant recipients with decompensated CPT B and CPT C cirrhosis.

Efficacy with HARVONI + RBV regimen has been established in adult CHC genotype 1 patients with decompensated cirrhosis, irrespective of transplantation status (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

Patients Co-infected with HIV-1

Efficacy with HARVONI has been established in adult CHC genotype 1 or 4 patients, with or without cirrhosis, co-infected with HIV-1 (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

CONTRAINDICATIONS

HARVONI is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

When HARVONI is administered with RBV, the contraindications to RBV also apply to this combination regimen. Refer to the RBV Product Monograph for a list of contraindications for RBV.

The use of RBV is contraindicated in pregnant women and in men whose female partners are pregnant, may be pregnant, or plan to become pregnant because of the risks for birth defects and fetal death associated with RBV (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Potential for Hepatitis B Virus (HBV) Reactivation**

Screen all patients for evidence of current or prior HBV infection before initiating HARVONI treatment. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct-acting antivirals (DAAs) in patients co-infected with HBV (see **WARNINGS AND PRECAUTIONS, Potential for Hepatitis B Virus Reactivation**).

General

Treatment with HARVONI should be initiated and monitored by a physician experienced in the management of chronic hepatitis C (CHC).

The safety and efficacy of HARVONI in combination with other anti-HCV medicines have not been studied. The sustained virologic response (SVR) of HARVONI is reduced in treatment-

experienced patients with HCV containing certain NS5A baseline mutations (see **MICROBIOLOGY**).

The safety and efficacy of HARVONI have not been studied in patients who have failed previous therapy with HARVONI.

Use with Potent P-gp Inducers

Medicinal products that are potent P-glycoprotein (P-gp) inducers [eg, rifampin, St. John's wort (*Hypericum perforatum*)] may significantly decrease ledipasvir and sofosbuvir plasma concentration leading to reduced therapeutic effect of HARVONI and potential loss of virologic response. Rifampin and St. John's wort should not be used with HARVONI (see **DRUG INTERACTIONS**).

Cardiovascular

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered HARVONI:

- Counsel patients about the risk of symptomatic bradycardia
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking HARVONI who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting HARVONI should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory

problems (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

Potential for Hepatitis B Virus Reactivation

Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV co-infected patients who were undergoing, or completed treatment containing DAAs. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patients with serologic evidence of resolved HBV infection (ie, HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Use with Certain HIV Antiretroviral Regimens

HARVONI has been shown to increase tenofovir exposure when used together with an HIV regimen containing tenofovir disoproxil fumarate (tenofovir DF) (see **DRUG INTERACTIONS**). Patients receiving HARVONI concomitantly with tenofovir DF, particularly those at increased risk for renal dysfunction should be monitored for tenofovir-associated adverse reactions. Refer to Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.

Coadministration with Related Products

HARVONI should not be administered concurrently with other medicinal products containing sofosbuvir (SOVALDI®, EPCLUSA™).

Hepatic

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir, and sofosbuvir. HARVONI can be administered in patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). Safety and efficacy of HARVONI have been established in adult genotype 1 CHC patients with decompensated cirrhosis. Safety and efficacy in liver transplant recipients with decompensated CPT C cirrhosis are based on the results seen in 17 patients.

Liver function monitoring (including direct bilirubin), when clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with HARVONI + RBV (see **ADVERSE EVENTS** and **CLINICAL TRIALS**).

Gastrointestinal

HARVONI contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption).

Renal

Renal impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with mild or moderate renal impairment. The safety of HARVONI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women

Pregnancy should be avoided while taking HARVONI as there are no data on the use of HARVONI in pregnant women. HARVONI should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their health care provider immediately in the event of a pregnancy.

In the rat and rabbit, at ledipasvir AUC exposures 5- and 2-fold higher, respectively, than the human exposure at 90 mg dose, no effects on fetal development were observed (see **TOXICOLOGY**).

In the ledipasvir rat pre- and postnatal study, at a maternally toxic dose, the developing rat offspring exhibited mean decreased body weight and body weight gain when exposed in utero (via maternal dosing) and during lactation (via maternal milk) at a maternal exposure approximately 4 times the exposure in humans at the recommended clinical dose. There were no effects on survival, physical and behavioral development, and reproductive performance in the offspring at maternal exposures similar to the exposure in humans at the recommended clinical dose (see **TOXICOLOGY**).

No effects on fetal development were observed in rats and rabbits at the highest doses of sofosbuvir tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 at the highest dose was approximately 6-fold and 16-fold the exposure in humans at the recommended clinical dose, respectively (see **TOXICOLOGY**).

Pregnancy and Concomitant Use with RBV

Ribavirin may cause birth defects and/or death of the exposed fetus (see **CONTRAINDICATIONS**). Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients when HARVONI is administered in combination with RBV as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to RBV.

HARVONI in combination with RBV should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use at least two effective forms of contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time (see the RBV product monograph).

Nursing Women

It is not known whether ledipasvir, sofosbuvir, and its metabolites are excreted in human breast milk. A risk to the newborn/infant cannot be excluded; therefore, nursing should be discontinued before treatment with HARVONI.

When administered to lactating rats, ledipasvir was detected in the plasma of suckling rats likely due to excretion of ledipasvir via milk. Ledipasvir plasma AUC ratio in the suckling rats to the lactating female rats was 0.26 on Lactation Day 10. Ledipasvir had no effects on the nursing pups.

Excretion of sofosbuvir in milk was studied in postpartum female rats after a single oral dose. The milk:plasma concentration ratios in the female rats were 0.1 at 1 hour post-dose and 0.8 at 24 hours post-dose. The predominant circulating metabolite GS-331007 was the primary component observed in the milk of lactating rats, and the metabolite had no effect on the nursing pups.

Pediatrics (< 18 years of age)

The safety and efficacy with HARVONI have been established in pediatric patients ≥ 12 years of age with genotype 1 CHC (see **CLINICAL TRIALS**).

The safety and efficacy of HARVONI in pediatric patients infected with other CHC genotypes or in patients who are < 12 years of age have not been established.

Geriatrics (≥ 65 years of age)

Clinical studies of HARVONI included 200 patients (8.7% of total number of patients in clinical trials) aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment groups. HARVONI can be administered in geriatric patients.

HCV/HBV Co-Infection:

The safety and efficacy of HARVONI have not been established in patients co-infected with HBV. HBV reactivation has been reported during treatment and post-treatment with DAAs in patients co-infected with HBV who were not undergoing treatment for HBV infection (see **WARNINGS AND PRECAUTIONS, Potential for HBV Reactivation**).

Patients Co-infected with HIV-1

In a clinical trial in HIV-1 co-infected adult patients, the relapse rate in Black patients was 9% (10/115), all of whom were IL28B non-CC genotype, and none in non-Black patients (0/220). In 3 clinical trials in HCV mono-infected patients, relapse rates were 3% (10/305) in Black patients and 2% (26/1637) in non-Black patients.

Monitoring and Laboratory Tests

Clearance of HCV may lead to increased replication of HBV in patients who are co-infected with HCV and HBV; co-infected patients should be monitored for clinical and laboratory signs (eg, HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS, Potential for HBV Reactivation**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety profile of HARVONI was established in the following patient populations: adult patients infected with HCV genotypes 1, 2, 3, 4, 5, or 6 who were treatment-naïve or who failed prior treatments (PEG-IFN/RBV or PI + PEG-IFN/RBV), and included a portion of patients with compensated cirrhosis; adult CHC genotype 1 or 4 patients co-infected with HIV-1; adult CHC patients who are post-liver transplant (genotype 1 or 4) and/or who have decompensated cirrhosis (genotype 1); and pediatric patients ≥ 12 years of age with genotype 1 CHC without cirrhosis or with compensated cirrhosis.

The safety assessment of HARVONI in patients with genotype 1 CHC is based on pooled data of 1080 patients from three Phase 3 clinical trials (ION-3, ION-1, and ION-2) including 215, 539, and 326 patients who received HARVONI for 8, 12, and 24 weeks, respectively.

The proportion of patients who permanently discontinued treatment due to adverse events was 0%, <1%, and 1% for patients receiving HARVONI for 8, 12, and 24 weeks, respectively. The

proportion of Grade 3 adverse events considered related to study drug by site investigators was 0% and 0.4% for 8 and 12 weeks, respectively; no Grade 4 adverse events were reported.

No adverse drug reactions specific to HARVONI have been identified.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trials in Adults (≥ 18 years of age)

The adverse reactions (Grades 2 to 4) observed in ≥ 2% of patients receiving 8, 12, or 24 weeks treatment with HARVONI in clinical trials are listed in Table 1.

Table 1. Adverse Reactions (Grades 2 – 4) Reported in ≥ 2% of Patients Receiving 8, 12, or 24 Weeks of HARVONI[a] from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)

	HARVONI 8 weeks	HARVONI 12 weeks	HARVONI 24 weeks
	N = 215	N = 539	N = 326
Headache	3%	4%	4%
Fatigue	2%	2%	5%

a Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Adverse reactions (Grades 2 to 4) occurring in less than 2% of patients receiving 8, 12, or 24 weeks treatment with HARVONI in clinical trials are listed below by body system:

Table 2. Adverse Reactions (Grades 2 – 4) Reported in < 2% of Patients Receiving 8, 12, or 24 Weeks of HARVONI[a] from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)

Body System	HARVONI 8, 12, or 24 Weeks[b]
Blood And Lymphatic System Disorders	Factor VIII inhibition
Cardiac Disorders	Palpitations
Eye Disorders	Visual impairment
Gastrointestinal Disorders	Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhoea, dyspepsia, gastrooesophageal reflux disease, mesenteric vein thrombosis, nausea, oral discomfort, vomiting
General Disorders And Administration Site Conditions	Asthenia, feeling abnormal, irritability, edema
Hepatobiliary Disorders	Hepatitis acute
Infections And Infestations	Conjunctivitis infective, salpingitis, sinusitis
Injury, Poisoning And Procedural Complications	Contusion, ligament sprain, meniscus injury, muscle strain
Metabolism and Nutrition Disorders	Abnormal loss of weight, decreased appetite, gout
Musculoskeletal and Connective Tissue Disorders	Arthralgia, joint effusion, muscle spasms, muscular weakness
Nervous System Disorders	Disturbance in attention, dizziness, memory impairment, migraine, migraine with aura, parosmia, somnolence
Psychiatric Disorders	Affect lability, aggression, anxiety, depressed mood, depression, emotional disorder, insomnia, libido decreased, sleep disorder
Renal And Urinary Disorders	Urinary retention
Reproductive System and Breast Disorders	Erectile dysfunction, metrorrhagia
Respiratory, Thoracic and Mediastinal Disorders	Oropharyngeal pain, sinus congestion
Skin And Subcutaneous Tissue Disorders	Acne, alopecia, hyperhidrosis, prurigo, pruritus, rash
Vascular Disorders	Hemorrhage, hypertension

a Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

b Note: adverse events have not been distinguished by whether they occurred during 8, 12, or 24 weeks of therapy.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

The frequency of treatment-emergent laboratory abnormalities (Grades 2-4) occurring in at least 2% of patients receiving 8, 12, or 24 Weeks of Treatment with HARVONI are described in Table 3.

Table 3. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 2% of Patients Receiving 8, 12, or 24 Weeks of HARVONI from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)

Laboratory Abnormality Parameters	HARVONI 8 weeks	HARVONI 12 weeks	HARVONI 24 weeks
	N = 215	N = 538*	N = 325*
Neutrophils (<1.0 x 10^9/L)	< 1%	< 1%	3%
Platelets (< 100 x 10^9/L)	0	2%	5%
Lipase (> 1.5 x ULN)	4%	6%	9%
Serum glucose (Hyperglycemia) (> 160 mg/dL)	9%	10%	12%
Serum glucose (Hypoglycemia) (< 55 mg/dL)	< 1%	2%	2%
Total Bilirubin (> 1.5 x ULN)	3%	< 1%	2%

* One patient was dosed but did not have any post-baseline lab values and was therefore excluded from the analysis.
ULN = Upper Limit of Normal

All patients with grades 2 to 4 elevations in lipase were asymptomatic, and the elevations were generally transient, with no treatment emergent clinical events of pancreatitis.

All patients with Grade 3 or 4 increased serum glucose had either a medical history of diabetes or glucose intolerance (HbA1c > 6.0%) at screening.

Patients with Cirrhosis

The safety assessment of HARVONI with or without ribavirin (RBV) was based on a randomized, double-blind and placebo-controlled trial in treatment-experienced genotype 1 patients with compensated cirrhosis and was compared to placebo in the SIRIUS trial. Patients were randomized to receive 24 weeks of HARVONI once daily by mouth without RBV or 12 weeks of placebo followed by 12 weeks of HARVONI once daily by mouth + RBV [see **CLINICAL TRIALS** section]. Table 4 presents the adverse reactions, as defined above, that occurred with at least 5% greater frequency in patients treated with 24 weeks of HARVONI or

12 weeks of HARVONI+RBV, compared to those reported for 12 weeks of placebo. The majority of the adverse reactions presented in Table 4 were Grade 1 or 2 in severity.

Table 4 **Adverse Reactions Reported ≥5% Greater Frequency in Treatment-Experienced Patients with Cirrhosis Receiving HARVONI[a] for 24 Weeks or HARVONI+RBV for 12 Weeks Compared to Placebo for 12 weeks**

	HARVONI 24 weeks (N=78)	HARVONI+RBV 12 weeks (N=76)	Placebo 12 weeks (N=77)
Asthenia	31%	34%	23%
Headache	29%	13%	16%
Fatigue	18%	4%	1%
Cough	5%	11%	1%
Myalgia	9%	4%	0
Dyspnea	3%	9%	1%
Irritability	8%	7%	1%
Dizziness	5%	1%	0

a Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Patients with other HCV Genotypes

The safety assessment of HARVONI in genotype 2 patients is based on study GS-US-337-1468 (LEPTON) that included 26 treatment-naïve or treatment-experienced genotype 2 patients who received 12 weeks of HARVONI. For genotype 3 patients, the safety assessment is based on study GS-US-337-0122 (ELECTRON-2) that included 101 treatment-naïve or treatment-experienced patients, with or without cirrhosis. Treatment-naïve patients were treated with HARVONI or HARVONI + RBV for 12 weeks; all treatment-experienced patients received HARVONI + RBV for 12 weeks. For genotype 4 patients (other than those included in SOLAR-1 or SOLAR-2, above), the safety assessment is based on pooled clinical trial data from studies GS-US-337-1119 (N=44) and GS-US-337-0115 (ION-4, N=8) that included 52 genotype 4 treatment-naïve or treatment-experienced patients who received HARVONI for 12 weeks. For genotype 5 and 6 patients, safety assessments are based on two phase 2 clinical trials [GS-US-337-1119 and GS-US-337-0122 (ELECTRON-2)] that included 41 and 25 patients for genotypes 5 and 6, respectively.

The safety profile associated with the use of HARVONI±RBV in nongenotype 1 CHC did not differ from the safety profile observed in patients with genotype 1 CHC. No adverse drug reactions specific to HARVONI were identified from the clinical trials conducted in subjects with genotype 2, 3, 4, 5 or 6 CHC.

Special Populations

Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

The safety of HARVONI+RBV was assessed in adult liver transplant recipients and/or patients with decompensated liver disease in two Phase 2 open-label trials in which patients received HARVONI+RBV for 12 (N=336) or 24 weeks (N=334).

The observed adverse events were consistent with expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known toxicity profile of RBV. One adverse event of direct bilirubin increased, where drug induced liver injury (DILI) could not be excluded and which resulted in permanent discontinuation of HARVONI, was reported in a liver transplant recipient with decompensated CPT B cirrhosis. This event, however, occurred at Week 20 of treatment with HARVONI and RBV, which is past the recommended dosing period of 12 weeks (see **WARNINGS AND PRECAUTIONS, Hepatic**).

Decreases in hemoglobin to less than 10 mg/dL and 8.5 mg/dL during treatment were experienced by 39% and 13% of patients treated with HARVONI+RBV, respectively. Ribavirin was discontinued in 15% of the patients.

HIV-1 Co-infected Patients

The safety of HARVONI was assessed in an open-label trial of 335 adult patients with HCV/HIV-1 co-infection who were on stable antiretroviral therapy (see **CLINICAL TRIALS**). The safety profile in HCV/HIV-1 co-infected patients was similar to that observed in HCV mono-infected patients. The most common adverse reactions occurring in at least 10% of patients were headache (20%) and fatigue (17%). No adverse reactions specific to HARVONI were identified.

Pediatrics (≥ 12 years of age)

The safety assessment of HARVONI in pediatric patients ≥ 12 years of age is based on data from an ongoing Phase 2, open-label clinical trial (GS-US-337-1116) that enrolled 100 patients, who were treated with HARVONI for 12 weeks. The adverse reactions observed were consistent with those observed in clinical studies of HARVONI in adults (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions**).

Post-Market Adverse Drug Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions have been identified during post approval use of HARVONI. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders
Serious symptomatic bradycardia when amiodarone is coadministered with HARVONI (see **WARNINGS AND PRECAUTIONS, Cardiovascular**, and **DRUG INTERACTIONS**).

Skin and Subcutaneous Tissue Disorders

Angioedema and skin rashes (sometimes with blisters or angioedema-like swelling).

DRUG INTERACTIONS

Overview

As HARVONI contains ledipasvir and sofosbuvir, any interactions that have been identified with these agents individually may occur with HARVONI.

After oral administration of HARVONI, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. Hydrolytic prodrug cleavage and sequential phosphorylation steps result in formation of the pharmacologically active uridine nucleoside analog triphosphate. Dephosphorylation of nucleotide metabolites results in conversion to the predominant circulating metabolite GS-331007 that accounts for approximately 85% of total systemic exposure. In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

Drug-Drug Interactions

Potential for HARVONI to Affect Other Drugs

Ledipasvir is a weak inhibitor of intestinal efflux drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir is an inhibitor of hepatic uptake transporters OATP1B1, OATP1B3, and hepatic efflux transporter BSEP only at concentrations exceeding those achieved in clinic. Ledipasvir is not an inhibitor of renal efflux transporters MRP2, MRP4, MATE1, renal uptake transporters OCT2, OAT1, OAT3, and hepatic uptake transport OCT1. Ledipasvir inhibits UGT1A1 only at concentrations exceeding those achieved in the clinic. The drug-drug interaction potential of ledipasvir is primarily limited to the process of intestinal absorption.

Sofosbuvir and GS-331007 are not relevant inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3, OCT1, and GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1 (see **DETAILED PHARMACOLOGY**).

Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Potential for Other Drugs to Affect HARVONI

Ledipasvir and sofosbuvir are substrates of efflux drug transporters P-gp and BCRP while GS-331007 is not. Drugs that are potent P-gp inducers (eg, rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of HARVONI and potential loss of virologic response, and should not be used with HARVONI (see **WARNINGS AND PRECAUTIONS**). Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir and ledipasvir plasma concentrations without increasing GS-331007 plasma concentration; HARVONI may therefore be coadministered with P-gp and/or BCRP inhibitors. Neither ledipasvir nor sofosbuvir is a substrate for hepatic uptake transporters

OCT1, OATP1B1, or OATP1B3. GS-331007 is not a substrate for renal uptake transporters including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2.

Ledipasvir is subject to slow oxidative metabolism via an unknown mechanism. *In vitro*, no detectable metabolism of ledipasvir by CYP enzymes has been observed. Biliary excretion of unchanged ledispavir is a major route of elimination. Sofosbuvir is not a substrate for CYP and UGT1A1 enzymes. Clinically significant drug interactions with HARVONI mediated by CYP or UGT1A1 enzymes are not expected.

Table 5 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either HARVONI, the components of HARVONI (ledipasvir and sofosbuvir) as individual agents, or are predicted drug interactions that may occur with HARVONI. The table is not all-inclusive (see **ACTION AND CLINICAL PHARMACOLOGY**).

Table 5. Established and Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid Reducing Agents:	↓ ledipasvir	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (eg, aluminum and magnesium hydroxide)		It is recommended to separate antacid and HARVONI administration by 4 hours.
H_2-receptor antagonists[c] (eg, famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (eg, omeprazole)		Proton-pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with HARVONI. Proton-pump inhibitors should not be taken before HARVONI.
Antiarrhythmics: amiodarone	Effect on amiodarone, ledipasvir, and sofosbuvir concentrations unknown	Coadministration of amiodarone with HARVONI may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended; if coadministration is required, cardiac monitoring is recommended (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).
digoxin	↑ digoxin	Coadministration of HARVONI with digoxin may result in increased plasma concentration of digoxin due to intestinal inhibition of P-gp by LDV. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended to obtain the desired clinical effect when coadministered with HARVONI.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[c]	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with rifabutin is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. HARVONI should not be used with rifampin, a potent P-gp inducer (see **WARNINGS AND PRECAUTIONS, General, Use with Potent P-gp Inducers)**
Antiretrovirals: Regimens containing tenofovir disoproxil fumarate (tenofovir DF)[c]	↑ tenofovir	HARVONI has been shown to increase tenofovir exposure. Patients receiving tenofovir DF and HARVONI concomitantly should be monitored for adverse reactions associated with tenofovir DF. Refer to the Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.
Other HIV Antiretrovirals tipranavir/ritonavir	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: simeprevir[c]	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased significantly when simeprevir is coadministered with ledipasvir. Coadministration is not recommended.
HMG-CoA Reductase Inhibitors rosuvastatin	↑ rosuvastatin	Coadministration of HARVONI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of HARVONI with rosuvastatin is not recommended.

a. This table is not all inclusive.

b. ↑ = increase, ↓ = decrease.

c These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with HARVONI

Based on drug interaction studies conducted with the components of HARVONI (ledipasvir or sofosbuvir) or HARVONI, no clinically significant drug interactions have been either observed or are expected when HARVONI is used with the following drugs: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, emtricitabine, efavirenz, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, or verapamil. For use of HARVONI with certain HIV regimens containing tenofovir DF, see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**, Table 5.

Assessment of Drug Interactions

The drug interaction studies described were conducted with HARVONI, or components of HARVONI (ledipasvir or sofosbuvir).

The effects of coadministered drugs on the exposure of ledipasvir, sofosbuvir, and GS-331007 are shown in Table 6. The effects of ledipasvir or sofosbuvir on the exposure of coadministered drugs are shown in Table 7.

Table 6. Drug Interactions: Changes in Pharmacokinetic Parameters for Ledipasvir, Sofosbuvir, and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir, and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Anti-HCV Drugs								
Simeprevir[h]	150 once daily	30 once daily[g]	ND	22	ledipasvir	1.81 (1.69, 2.94)	1.92 (1.77, 2.07)	NA
Anti-HIV Drugs								
Abacavir/ lamivudine	600/300 once daily	90 once daily	400 once daily	13	ledipasvir	1.10 (1.01, 1.19)	1.18 (1.10, 1.28)	1.26 (1.17, 1.36)
					sofosbuvir	1.08 (0.85, 1.35)	1.21 (1.09, 1.35)	NA
					GS-331007	1.00 (0.94, 1.07)	1.05 (1.01, 1.09)	1.08 (1.01, 1.14)
Atazanavir/ ritonavir	300/100 once daily	90 once daily	400 once daily	30	ledipasvir	1.98 (1.78, 2.20)	2.13 (1.89, 2.40)	2.36 (2.08, 2.67)
					sofosbuvir	0.96 (0.88, 1.05)	1.08 (1.02, 1.15)	NA
					GS-331007	1.13 (1.08, 1.19)	1.23 (1.18, 1.29)	1.28 (1.21, 1.36)
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF	300/100/200/300 once daily simultaneously with HARVONI[b]	90 once daily	400 once daily	24	ledipasvir	1.68 (1.54, 1.84)	1.96 (1.74, 2.21)	2.18 (1.91, 2.50)
					sofosbuvir	1.01 (0.88, 1.15)	1.11 (1.02, 1.21)	NA
					GS-331007	1.17 (1.12, 1.23)	1.31 (1.25, 1.36)	1.42 (1.34,

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir, and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
								1.49)
Darunavir/ ritonavir[h]	800/100 once daily	90 once daily	ND	23	ledipasvir	1.45 (1.34, 1.56)	1.39 (1.28, 1.49)	1.39 (1.29, 1.51)
		ND	400 single dose	18	sofosbuvir	1.45 (1.10, 1.92)	1.34 (1.12, 1.59)	NA
					GS-331007	0.97 (0.90, 1.05)	1.24 (1.18, 1.30)	NA
Darunavir/ ritonavir + emtricitabine/ tenofovir disoproxil fumarate	800/100/200/300 once daily simultaneously with HARVONI[b]	90 once daily	400 once daily	23	ledipasvir	1.11 (0.99, 1.24)	1.12 (1.00, 1.25)	1.17 (1.04, 1.31)
					sofosbuvir	0.63 (0.52, 0.75)	0.73 (0.65, 0.82)	NA
					GS-331007	1.10 (1.04, 1.16)	1.20 (1.16, 1.24)	1.26 (1.20, 1.32)
Dolutegravir + emtricitabine/ tenofovir DF	50 + 200/300 once daily	90 once daily	400 once daily	29	ledipasvir	0.85 (0.81, 0.90)	0.89 (0.84, 0.95)	0.89 (0.84, 0.95)
					sofosbuvir	1.06 (0.92, 1.21)	1.09 (1.00, 1.19)	NA
					GS-331007	0.99 (0.95, 1.03)	1.06 (1.03, 1.09)	1.06 (1.03, 1.10)
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate[c]	600/200/300 once daily	90 once daily	400 once daily	14	ledipasvir	0.66 (0.59, 0.75)	0.66 (0.59, 0.75)	0.66 (0.57, 0.76)
					sofosbuvir	1.03 (0.87, 1.23)	0.94 (0.81, 1.10)	NA
					GS-331007	0.86 (0.76, 0.96)	0.90 (0.83, 0.97)	1.07 (1.02, 1.13)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide	150/150/200/10 once daily	90 once daily	400 once daily	30	ledipasvir	1.65 (1.53,1.78)	1.79 (1.64,1.96)	1.93 (1.74, 2.15)
					sofosbuvir	1.28 (1.13,1.47)	1.47 (1.35,1.59)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir, and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
					GS-331007	1.29 (1.24,1.35)	1.48 (1.44,1.53)	1.66 (1.60, 1.73)
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate[e]	200/25/300 once daily	90 once daily	400 once daily	15	ledipasvir	1.01 (0.95, 1.07)	1.08 (1.02, 1.15)	1.16 (1.08, 1.25)
					sofosbuvir	1.05 (0.93, 1.20)	1.10 (1.01, 1.21)	NA
					GS-331007	1.06 (1.01, 1.11)	1.15 (1.11, 1.19)	1.18 (1.13, 1.24)
Raltegravir[h]	400 twice daily	90 once daily	ND	28	ledipasvir	0.92 (0.85, 1.00)	0.91 (0.84, 1.00)	0.89 (0.81, 0.98)
		ND	400 single dose	19	sofosbuvir	0.87 (0.71, 1.08)	0.95 (0.82, 1.09)	NA
					GS-331007	1.09 (0.99, 1.19)	1.02 (0.97, 1.08)	NA
Anti-infectives								
Rifampin[h]	600 once daily	90 single dose[f]	ND	31	ledipasvir	0.65 (0.56, 0.76)	0.41 (0.36, 0.48)	NA
		ND	400 single dose	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
					GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir, and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
H2-Receptor Antagonists								
Famotidine	40 single dose simultaneously with HARVONI	90 single dose	400 single dose	12	ledipasvir	0.80 (0.69, 0.93)	0.89 (0.76, 1.06)	NA
					sofosbuvir	1.15 (0.88, 1.50)	1.11 (1.00, 1.24)	NA
					GS-331007	1.06 (0.97, 1.14)	1.06 (1.02, 1.11)	NA
	40 single dose 12 hours prior to HARVONI			12	ledipasvir	0.83 (0.69, 1.00)	0.98 (0.80, 1.20)	NA
					sofosbuvir	1.00 (0.76, 1.32)	0.95 (0.82, 1.10)	NA
					GS-331007	1.13 (1.07, 1.20)	1.06 (1.01, 1.12)	NA
Immunosuppressants								
Cyclosporine[h]	600 single dose	ND	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
Tacrolimus[h]	5 single dose	ND	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA
Opiate Agonist								
Methadone[h]	30 to 130 daily	ND	400 once daily	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir, and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Proton Pump Inhibitors								
Omeprazole	20 once daily simultaneously with HARVONI	90 single dose	400 single dose	16	ledipasvir	0.89 (0.61, 1.30)	0.96 (0.66, 1.39)	NA
					sofosbuvir	1.12 (0.88, 1.42)	1.00 (0.80, 1.25)	NA
					GS-331007	1.14, (1.01, 1.29)	1.03 (0.96, 1.12)	NA
	20 once daily 2 hours prior to ledipasvir	30 single dose	ND	17	ledipasvir	0.52 (0.41, 0.66)	0.58 (0.48, 0.71)	NA

NA = not available/not applicable, ND = not dosed.

a All interaction studies conducted in healthy volunteers.

b Staggered administration (12 hours apart) of atazanavir/ritonavir+emtricitabine/tenofovir DF or darunavir/ritonavir+emtricibatine/tenofovir DF and HARVONI provided similar results.

c Administered as ATRIPLA®.

d This study was conducted to support the use of STRIBILD.

e Administered as COMPLERA®.

f This study was conducted in the presence of two other investigational HCV direct-acting agents.

g Ledipasvir dose administered in this study is 30 mg which is lower than the ledipasvir dose of 90 mg when administered as HARVONI.

h These studies have not been performed with HARVONI; they were conducted with either ledipasvir or sofosbuvir administered as single agents.

Table 7. Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Ledipasvir, Sofosbuvir, or HARVONI[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir dose (mg)	Sofos-buvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir, or HARVONI No Effect=1.00		
					C_{max}	AUC[c]	C_{min}
Anti-HCV							
Simeprevir[f]	150 once daily	30 once daily[e]	ND	28	2.61 (2.39, 2.86)	2.69 (2.44, 2.96)	NA
Anti-HIV							
Abacavir /lamivudine	abacavir 600 once daily	90 once daily	400 once daily	15	0.92 (0.87, 0.97)	0.90 (0.85, 0.94)	NA
	lamivudine 300 once daily				0.93 (0.87, 1.00)	0.94 (0.90, 0.98)	1.12 (1.05, 1.20)
Atazanavir/ ritonavir[g]	atazanavir 300 once daily	90 once daily	400 once daily	30	1.07 (1.00, 1.15)	1.33 (1.25, 1.42)	1.75 (1.58, 1.93)
	ritonavir 100 once daily				0.93 (0.84, 1.02)	1.05 (0.98, 1.11)	1.56 (1.42, 1.71)
Atazanavir/ ritonavir + emtricitabine/ tenofovir disoproxil fumarate[g] simultaneously with HARVONI[h]	atazanavir 300 once daily[i]	90 once daily	400 once daily	24	1.07 (0.99, 1.14)	1.27 (1.18, 1.37)	1.63 (1.45, 1.84)
	ritonavir 100 once daily				0.86 (0.79, 0.93)	0.97 (0.89, 1.05)	1.45 (1.27, 1.64)
	emtricitabine 200 once daily[i]				0.98 (0.94, 1.02)	1.00 (0.97, 1.04)	1.04 (0.96, 1.12)
	enofovir disoproxil fumarate 300 once daily[i]				1.47 (1.37, 1.58)	1.35 (1.29, 1.42)	1.47 (1.38, 1.57)

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir, or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
Darunavir (boosted by ritonavir[f,g])	800/100 once daily	90 once daily	ND	23	1.02 (0.88, 1.19)	0.96 (0.84, 1.11)	0.97 (0.86, 1.10)
		ND	400 single dose	18	0.97 (0.94, 1.01)	0.97 (0.94, 1.00)	0.86 (0.78, 0.96)
Darunavir/ ritonavir + emtricitabine/ tenofovir disoproxil fumarate simultaneously with HARVONI[h]	darunavir 800 once daily[j]	90 once daily	400 once daily	23	1.01 (0.96, 1.06)	1.04 (0.99, 1.08)	1.08 (0.98, 1.20)
	ritonavir 100 once daily				1.17[j] (1.01, 1.35)	1.25[j] (1.15, 1.36)	1.48[j] (1.34, 1.63)
	emtricitabine 200 once daily[j]				1.02 (0.96, 1.08)	1.04 (1.00, 1.08)	1.03 (0.97, 1.10)
	tenofovir disoproxil fumarate 300 once daily[j]				1.64 (1.54, 1.74)	1.50 (1.42, 1.59)	1.59 (1.49, 1.70)
Dolutegravir + emtricitabine/ tenofovir DF[k]	dolutegravir 50 once daily	90 once daily	400 once daily	29	1.15 (1.07, 1.23)	1.13 (1.06, 1.20)	1.13 (1.06, 1.21)
	emtricitabine 200 once daily				1.02 (0.95, 1.08)	1.07 (1.04, 1.10)	1.05 (1.02, 1.09)
	tenofovir DF 300 once daily				1.61 (1.51, 1.72)	1.65 (1.59, 1.71)	2.15 (2.05, 2.26)
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate[b]	efavirenz 600 once daily	90 once daily	400 once daily	15	0.87 (0.79, 0.97)	0.90 (0.84, 0.96)	0.91 (0.83, 0.99)
	emtricitabine 200 once daily				1.08 (0.97, 1.21)	1.05 (0.98, 1.11)	1.04 (0.98, 1.11)
	tenofovir disoproxil fumarate 300 once daily				1.79 (1.56, 2.04)	1.98 (1.77, 2.23)	2.63 (2.32, 2.97)

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir, or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide	elvitegravir 150 once daily	90 once daily	400 once daily	30	0.98 (0.90, 1.07)	1.11 (1.02, 1.20)	1.46 (1.28, 1.66)
	cobicistat 150 once daily				1.23 (1.15, 1.32)	1.53 (1.45, 1.62)	3.25 (2.88, 3.67)
	emtricitabine 200 once daily				1.03 (0.96, 1.11)	0.97 (0.93, 1.00)	0.95 (0.91, 0.99)
	tenofovir alafenamide 10 once daily				0.90 (0.73, 1.11)	0.86 (0.78, 0.95)	NA
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate[d]	emtricitabine once 200 daily	90 once daily	400 once daily	14	1.02 (0.98, 1.06)	1.05 (1.02, 1.08)	1.06 (0.97, 1.15)
	rilpivirine 25 once daily				0.97 (0.88, 1.07)	1.02 (0.94, 1.11)	1.12 (1.03, 1.21)
	tenofovir disoproxil fumarate 300 once daily				1.32 (1.25, 1.39)	1.40 (1.31, 1.50)	1.91 (1.74, 2.10)
Raltegravir[f]	400 twice daily	90 once daily	ND	28	0.82 (0.66, 1.02)	0.85 (0.70, 1.02)	1.15 (0.90, 1.46)
		ND	400 single dose	19	0.57 (0.44, 0.75)	0.73 (0.59, 0.91)	0.95 (0.81, 1.12)

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir dose (mg)	Sofos-buvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir, or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
Estrogen-based Contraceptives							
Norelgestromin	Norgestimate 0.180/0.215/0.250/ ethinyl estradiol 0.025 once daily[f]	90 once daily	ND	15	1.02 (0.89, 1.16)	1.03 (0.90, 1.18)	1.09 (0.91, 1.31)
		ND	400 once daily		1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel		90 once daily	ND		1.03 (0.87, 1.23)	0.99 (0.82, 1.20)	1.00 (0.81, 1.23)
		ND	400 once daily		1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol		90 once daily	ND		1.40 (1.18, 1.66)	1.20 (1.04, 1.39)	0.98 (0.79, 1.22)
		ND	400 once daily		1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Immunosuppressants							
Cyclosporine[f]	600 single dose	ND	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
Tacrolimus[f]	5 single dose	ND	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Opiate Agonists							
R-Methadone[f]	30 to 130 daily	ND	400 once daily	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone[f]					0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)

NA = not available/not applicable, ND = not dosed.
a All interaction studies conducted in healthy volunteers.
b Administered as ATRIPLA.
c This study was conducted to support the use of STRIBILD.
d Administered as COMPLERA.

e Ledipasvir dose administered in this study was 30 mg which is lower than the ledipasvir dose of 90 mg when administered as HARVONI.
f These studies have not been performed with HARVONI; they were conducted with either ledipasvir or sofosbuvir administered as single agents.
g Ledipasvir leads to moderate increases of ritonavir plasma exposures.
h Staggered administration (12 hours apart) of atazanavir/ritonavir+emtricitabine/tenofovir DF or darunavir/ritonavir+emtricitabine/tenofovir DF and HARVONI provided similar results.
i Comparison based on exposures when administered as atazanavir/ritonavir+emtricitabine/tenofovir DF.
j Comparison based on exposures when administered as darunavir/ritonavir+emtricitabine/tenofovir DF.
k Comparison based on exposures when administered as dolutegravir + emtricitabine/tenofovir DF

Drug-Food Interactions

The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without food. HARVONI can be administered without regard to food.

Relative to fasting conditions, the administration of a single dose of HARVONI with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal did not substantially affect the sofosbuvir C_{max} and AUC_{inf}. The exposures of GS-331007 and ledipasvir were not altered in the presence of either meal type. (see **DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics** and **DETAILED PHARMACOLOGY).**

Drug-Herb Interactions

St. John's wort should not be used with HARVONI.

Coadministration of St. John's wort, a potent P-gp inducer, may decrease ledipasvir and sofosbuvir plasma concentrations, which may result in loss of therapeutic effect. See **WARNINGS AND PRECAUTIONS, General, Use with Potent P-gp Inducers**.

Drug-Laboratory Interactions

Interactions of HARVONI with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The treatment duration of HARVONI is fixed and is not guided by a patient's HCV RNA levels (ie, no response guided therapy).

Recommended Dose and Dosage Adjustment in Adults (≥ 18 years of age)

HARVONI is a fixed dose single tablet regimen. No dosage adjustments are possible for HARVONI.

The recommended dose of HARVONI is one tablet of 90 mg/400 mg ledipasvir/sofosbuvir, taken orally, once daily with or without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

The recommended dose and treatment duration for HARVONI in adult patients (≥ 18 years of age) is provided in Table 8.

Table 8. Treatment Dose and Duration for HARVONI in HCV-infected Adult Patients

	Patient Population	Treatment Regimen and Duration
Genotype 1	Treatment-naïve[a] with or without cirrhosis[b]	HARVONI 8 or 12 weeks[c]
	Treatment-experienced[d] without cirrhosis[b]	HARVONI 12 weeks
	Treatment-experienced[d] with cirrhosis[b]	HARVONI 24 weeks[e]
	Treatment-naïve[a] and treatment-experienced[d] with decompensated cirrhosis (Child-Pugh B or C)	HARVONI + RBV[e] 12 weeks
Genotype 1 or 4	Treatment-naïve[a] and treatment-experienced[d] liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	HARVONI + RBV[f] 12 weeks
Genotype 1 or 4	Treatment-naïve[a] and treatment-experienced[d] HCV/HIV-1 co-infected patients, with or without cirrhosis[b]	HARVONI 12 weeks[h]
Genotype 2, 4, 5 or 6	Treatment-naïve[a] and treatment-experienced[d], with or without cirrhosis[b]	HARVONI 12 weeks
Genotype 3	Treatment-naïve[a] with or without cirrhosis[b]	HARVONI + RBV[f] 12 weeks
	Treatment-experienced[d] with or without cirrhosis[b]	HARVONI + RBV[f] 24 weeks

a. Treatment-naïve is defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent at the time of treatment initiation.

b. Cirrhosis is defined as any one of the following: Liver biopsy showing cirrhosis (eg, Metavir score = 4 or Ishak score ≥ 5); or Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa; or FibroTest® score of > 0.75 and an aspartate aminotransferase (AST): platelet ratio index (APRI) of > 2.

c. HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL (see **CLINICAL TRIALS**).

d. Treatment-experienced is defined as those who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor.

e. HARVONI+RBV[f] for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for RBV.

f. The daily dose of RBV is weight based (<75 kg = 1000 mg; ≥75 kg = 1200 mg) and administered orally in two divided doses with food. Refer to RBV PM for information on dose modification.

g. Administer ribavirin at a starting daily dosage of 600 mg in two divided doses with food. If the starting dosage is well-tolerated, the dosage can be titrated up to a maximum of 1000-1200 mg daily divided (<75 kg = 1000 mg; ≥75 kg = 1200 mg) and administered twice daily with food If the starting dosage is not well-tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels. Refer to RBV PM for information on dose modifications.

h. Refer to Tables 5-7 for dosing recommendations with HIV-1 antiviral agents and for observed drug exposure levels when co-administered with HIV antiviral agents. **(DRUG INTERACTIONS, Drug-Drug Interactions)**

Special Populations

Pediatrics (<18 Years of age)

In pediatric patients ≥ 12 years of age with genotype 1 CHC without cirrhosis or with compensated cirrhosis, the recommended dose of HARVONI is one tablet of 90 mg/400 mg ledipasvir/sofosbuvir, taken orally once daily with or without food for 12 weeks (see **CLINICAL TRIALS** and **ACTION AND CLINICAL PHARMACOLOGY**). No data are available to make a dose recommendation for pediatric patients < 12 years or ≥ 12 years of age with other genotypes.

HARVONI is not indicated for use in pediatric patients < 12 years of age.

Geriatrics (> 65 years of age)

HARVONI can be administered in elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Impairment

Renal impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with mild or moderate renal impairment. The safety of HARVONI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatic Impairment

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**). Safety and efficacy of HARVONI have been established in genotype 1 CHC adult patients with decompensated cirrhosis.

Missed Dose

If a patient misses a dose of HARVONI within 18 hours of the time it is usually taken, the patient should take HARVONI as soon as possible, and then take the next dose of HARVONI at the regularly scheduled time.

If a patient misses a dose of HARVONI and it is after 18 hours of the time it is usually taken, the patient should not take the missed dose, but resume the usual dosing schedule. A double dose of HARVONI must not be taken.

If a patient vomits less than 5 hours after taking a dose of HARVONI, the patient should take another dose of HARVONI. If a patient vomits more than 5 hours after taking a dose of HARVONI, the patient should take the next dose at the regularly scheduled time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No specific antidote is available for overdose with HARVONI. If overdose occurs the patient must be monitored for evidence of toxicity. Hemodialysis is unlikely to result in significant removal of ledipasvir since ledipasvir is highly bound to plasma protein. Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007.

Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance. General supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient are recommended.

The highest documented doses of ledipasvir and sofosbuvir were 120 mg twice daily for 10 days and a single dose of 1200 mg, respectively. In these trials, there were no untoward effects observed at this dose level, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

ACTION AND CLINICAL PHARMACOLOGY

Description

Ledipasvir is an HCV NS5A inhibitor. Sofosbuvir is a nucleotide analog pan-genotypic NS5B polymerase inhibitor.

Mechanism of Action

HARVONI

HARVONI is a fixed-dose single tablet regimen of ledipasvir and sofosbuvir.

Both sofosbuvir and ledipasvir exhibit high potency and specificity as individual agents against HCV as compounds that target the HCV NS5B and NS5A proteins, respectively. Both compounds display low cytotoxicity in a number of distinct cell lines and display no significant antiviral activity against other viruses tested. *In vitro* combination studies using both sofosbuvir and ledipasvir showed an additive effect as measured by *in vitro* cell based genotype 1a and 1b HCV replicon assays. As individual components, both sofosbuvir and ledispasvir showed additive to synergistic activity with all other anti-HCV agents.

Ledipasvir

Ledipasvir is a direct acting anti-viral agent that inhibits HCV RNA replication and virion production by targeting the HCV NS5A protein. The NS5A protein is thought to play multiple roles in mediating viral replication, host-cell interactions, and viral pathogenesis. As a nonstructural (NS) protein with no apparent enzymatic activity, NS5A functions through interaction with other viral and cellular proteins. The protein NS5A protein is critical for HCV viability and the rapid viral load (HCV RNA) decline produced by NS5A inhibitors has been postulated to be due to inhibition of viral replication (as with NS3 and NS5B inhibitors) and additional inhibition of virion assembly or secretion from infected cells. The HCV NS5A protein is phosphorylated on multiple sites by host cell kinases and interacts with host cell membranes. While no known enzymatic function has been ascribed to NS5A, it is an essential component of the HCV replicase. *In vitro* resistance selection and cross-resistance studies also indicate ledipasvir targets NS5A as its mode of action.

Sofosbuvir

Sofosbuvir is a pan-genotypic polymerase inhibitor of the HCV NS5B RNA-dependent RNA polymerase (RdRp). HCV NS5B is the essential initiating and catalytic subunit of the membrane-associated multiprotein complex that mediates HCV RNA replication and is critical for the viral replication cycle. There is no human homolog for HCV NS5B RdRp. Sofosbuvir is a monophosphorylated pyrimidine nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203). Incorporation of GS-461203 into nascent RNA strongly reduces the efficiency of further RNA elongation by RdRp, resulting in premature termination of RNA synthesis. The stopping of viral replication leads to a rapid decline of HCV viral load and clearing of HCV levels in the body.

Pharmacodynamics

Effect on Electrocardiogram

The thorough QT studies have been conducted with the individual drugs, ledipasvir and sofosbuvir.

The effect of ledipasvir 120 mg twice daily for 10 days on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) three period crossover thorough QT trial in 59 healthy subjects.

The effects of sofosbuvir at the therapeutic dose (400 mg) and 3-fold above therapeutic dose (1200 mg) on QTc interval were evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects.

These trials demonstrated a lack of effect of ledipasvir or sofosbuvir on prolongation of the QTcF interval. The upper bounds of the two-sided 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) were below 10 ms.

Pharmacokinetics

Ledipasvir AUC is dose proportional over the dose range of 3 to 100 mg. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg.

The pharmacokinetic properties of ledipasvir, sofosbuvir, and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in patients with chronic hepatitis C following oral administration of HARVONI.

The pharmacokinetics of HARVONI are shown in Table 9.

Table 9. Summary of Once-Daily Administration of HARVONI in Healthy Adult Subjects and HCV-Infected Patients

PK Parameters	Healthy Subjects[a] HARVONI N=192 Geometric Mean (Range)			HCV-Infected Patients[b] HARVONI N=2113 Geometric Mean (Range)		
	LDV[c]	SOF	GS-331007	LDV	SOF[d]	GS-331007
AUC_{0-24} (ng·h/mL)	9600 (1160, 36800)	1170 (505, 2470)	11400 (5660, 21300)	7290 (416, 49100)	1320 (511, 6690)	12000 (1790, 32000)
C_{max} (ng/mL)	476 (56.9, 1590)	563 (156, 1290)	826 (492, 1730)	323 (19.6, 1910)	618 (87.7, 2540)	707 (83.1, 1690)
C_{min} (ng/mL)	283 (33.5, 1180)	ND	ND	211 (13.4, 1550)	ND	ND

a. Population PK analysis from Phase 1 studies.
b. Population PK analysis from Phase 2 and 3 studies.
c. N=191, one subject did not have estimable PK parameters for LDV
d. N=1542; 571 subjects did not have estimable PK parameters for SOF
ND: not determined

Relative to healthy subjects, ledipasvir AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively in HCV-infected patients. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and patients with HCV infection.

Based on population PK analyses, age, race, BMI, treatment status (treatment-naïve or treatment-experienced), presence of RBV in the treatment regimen, or the presence or absence of cirrhosis had no clinically relevant effects on the exposure of SOF, GS-331007, or LDV.

Absorption

The pharmacokinetic properties of ledipasvir, sofosbuvir, and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration of HARVONI, ledipasvir median peak concentrations were observed 4.0 to 4.5 hours post-dose. Sofosbuvir was absorbed quickly and the peak median plasma concentration was observed ~ 0.8 to 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed between 3.5 to 4 hours post-dose.

Effects of Food

The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without food. Relative to fasting conditions, the administration of a single dose of HARVONI with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal did not alter the exposures of ledipasvir or GS-331007. Either meal type did not substantially affect the sofosbuvir C_{max} and AUC_{inf}. HARVONI can be administered without regard to food.

Distribution

Ledipasvir is >99.8% bound to human plasma proteins. After a single 90 mg dose of [^{14}C]-ledipasvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity ranged between 0.51 and 0.66, indicating radioactivity exclusion from erythrocytes.

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Metabolism

In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP 2C19, CYP2D6, and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90 mg [^{14}C]-LDV, systemic exposure was almost exclusively to the parent drug (> 98%). Unchanged ledipasvir is the major species present in feces.

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*.

Excretion

Following a single 90 mg oral dose of [^{14}C]-ledipasvir, mean total recovery of the [^{14}C]-radioactivity in feces and urine was approximately 87%, with most of the radioactive dose recovered from feces (approximately 86%). Unchanged ledipasvir excreted in feces accounted for a mean of 70% of the administered dose and the oxidative metabolite M19 accounted for 2.2% of the dose. These data suggest that biliary excretion of unchanged ledipasvir is a major route of elimination with renal excretion being a minor pathway (approximately 1%). The median terminal half-life of ledipasvir following administration of HARVONI was 47 hours.

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. This data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007, following administration of HARVONI, were 0.5 and 27 hours respectively.

Special Populations and Conditions

Pediatrics (< 18 years of age)

Ledipasvir, sofosbuvir, and GS-331007 exposures in pediatric patients ≥ 12 years of age were similar to those in adults from Phase 2/3 studies, following administration of HARVONI (90/400 mg). The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 have not been established in pediatric patients < 12 years of age.

Geriatrics (≥ 65 years of age)

Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 80 years) analyzed, age did not have a clinically relevant effect on the exposure to ledipasvir, sofosbuvir, or GS-331007. Clinical studies of HARVONI included 200 patients (8.7% of total patients in the clinical trials) aged 65 and over. The response rates observed for patients ≥65 years of age were similar to that of patients <65 years of age, across treatment groups.

Gender

AUC and C_{max} of ledipasvir were 77% and 58% higher respectively in females than males; however, the relationship between gender and ledipasvir exposures was not considered clinically relevant as high response rates (SVR >90%) were achieved in male and female patients across the Phase 3 studies. No clinically relevant pharmacokinetic differences have been observed between men and women for sofosbuvir and GS-331007.

Race

No clinically relevant pharmacokinetic differences due to race have been identified for ledipasvir, sofosbuvir, or GS-331007.

Hepatic Insufficiency

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of HARVONI have been established in genotype 1 CHC adult patients with decompensated cirrhosis (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative subjects with severe hepatic impairment (Child Pugh Class C). Ledipasvir plasma exposure (AUC_{inf}) was similar in subjects with severe hepatic impairment and matched control subjects with normal hepatic function. Mild or moderate hepatic impairment is not expected to alter HARVONI pharmacokinetics. No dose adjustment of ledipasvir is recommended for patients with mild, moderate, and severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of ledipasvir.

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate, and severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

Renal Insufficiency

Renal impairment studies have been conducted with the individual drugs, ledipasvir, and sofosbuvir. Data from these studies support the use of HARVONI in patients with mild or moderate renal impairment. The safety of HARVONI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault) and matched control subjects with normal renal function (eGFR ≥ 90 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment. No dose adjustment of ledipasvir is required for patients with mild, moderate, or severe renal impairment. An evaluation of ledipasvir pharmacokinetics in subjects with ESRD has not been conducted.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2), and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir. An increase in plasma exposure of sofosbuvir and its 2 metabolites of approximately 2-fold or less was observed in subjects with mild and moderate renal impairment compared with subjects with normal renal function. No dose adjustment is required for patients with mild or moderate renal impairment.

Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. Following a single 400 mg dose of sofosbuvir, a 4 hour hemodialysis session removed approximately 18% of administered dose. The safety and efficacy of sofosbuvir

has not been assessed in patients with severe renal impairment or ESRD (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**, and **DETAILED PHARMACOLOGY**).

STORAGE AND STABILITY

Store below 30 °C (86 °F).

- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HARVONI is a fixed-dose single tablet regimen containing ledipasvir and sofosbuvir for oral administration.

Each tablet contains 90 mg ledipasvir and 400 mg of sofosbuvir. The tablets include the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Yellow #6/sunset yellow FCF aluminum lake.

HARVONI is available as an orange colored, diamond shaped, film-coated tablet debossed with "GSI" on one side and "7985" on the other side of the tablet. Each bottle contains 28 tablets, a silica gel desiccant, polyester coil, and closed with a child resistant closure.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

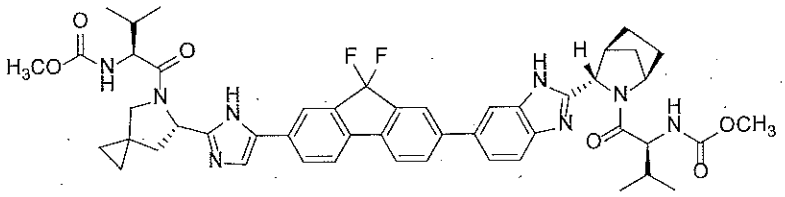
Proper name: **ledipasvir**

Chemical name: Methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7-{2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Molecular formula: $C_{49}H_{54}F_2N_8O_6$

Molecular mass: 889.00

Structural formula:



Physicochemical properties:

Solubility: Ledipasvir is practically insoluble (<0.1 mg/mL) across the pH range of 3.0-7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL).

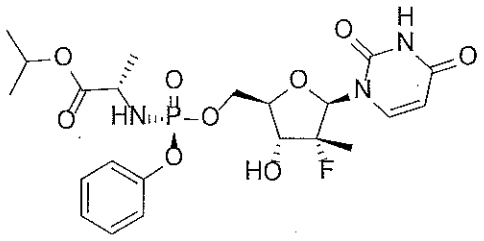
Proper name: **sofosbuvir**

Chemical name: (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate

Molecular formula: $C_{22}H_{29}FN_3O_9P$

Molecular mass: 529.45

Structural formula:



Physicochemical properties:

Appearance	Sofosbuvir is a white to off-white crystalline solid.
Solubility	Sofosbuvir is slightly soluble in water.

CLINICAL TRIALS

Adults

In clinical trials described in this section, the efficacy of HARVONI (±RBV) was evaluated in a total of 3399 patients with CHC.

The efficacy of HARVONI was evaluated in three Phase 3 trials with data available for a total of 1518 patients with genotype 1 CHC. All three trials evaluated the efficacy of HARVONI with or without RBV. The demographics and baseline characteristics for the patients in studies ION-3, ION-1, and ION-2 were well balanced across the treatment groups as summarized in Table 11, Table 15, and Table 19, respectively.

The efficacy of HARVONI in 335 HCV/HIV-1 co-infected patients with genotype 1 (n=327) or 4 (n=8) CHC, with or without cirrhosis, was evaluated in an open-label Phase 3 trial (ION-4). All patients in the trial were treated with HARVONI for 12 weeks.

Patients in all the above trials had compensated liver disease.

The efficacy of HARVONI in liver transplant recipients and/or patients with decompensated cirrhosis was evaluated in two open-label Phase 2 trials (SOLAR-1 and SOLAR-2) that enrolled patients with genotype 1 (N=628) and 4 (N=42) CHC post-liver transplant and/or with decompensated cirrhosis. Patients in the two trials were treated with HARVONI+RBV for 12 or 24 weeks.

Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate which was defined as HCV RNA less than Lower Limit of Quantitation (LLOQ) at 12 weeks after the cessation of treatment.

Clinical Trials in Patients with Genotype 1 CHC

Treatment-Naïve Patients without Cirrhosis [ION-3 (Study 0108)]

Trial Design

The trial design of Study ION-3 is described in Table 10.

Table 10. Summary of Trial Design in Treatment Naïve[a] Patients without Cirrhosis (ION-3)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	HARVONI (90 mg/400 mg), QD, PO +/- RBV 1000 or 1200 mg/day, BID, PO	HARVONI	8 weeks
		HARVONI + RBV	8 weeks
		HARVONI	12 weeks

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day

a. Patients were treatment naïve (defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent at the time of enrollment), non-cirrhotic, with genotype 1 CHC. Patients were randomized in a 1:1:1 ratio to one of the three treatment groups and stratified by HCV genotype (1a vs. 1b).

Demographics and Other Baseline Characteristics

Demographic characteristics for patients in ION-3 are provided in Table 11.

Table 11. Demographic and Other Baseline Characteristics of HCV Treatment-Naïve Patients without Cirrhosis (ION-3)

Characteristics	HARVONI 8 Weeks N= 215 n (%)	HARVONI + RBV 8 Weeks N = 216 n (%)	HARVONI 12 Weeks N = 216 n (%)	Total N = 647 n (%)
Age (years)				
Mean (range)	53 (20-75)	51 (21-75)	53 (20-71)	52 (20-75)
Gender				
Male	130 (60)	117 (54)	128 (59)	375 (58)
Female	85 (40)	99 (46)	88 (41)	272 (42)
Race				
White	164 (76)	176 (82)	167 (77)	507 (78)
Black	45 (21)	36 (17)	42 (19)	123 (19)
Asian	5 (2)	2 (1)	3 (1)	10 (2)
Other	1 (1)	2 (1)	4 (2)	7 (1)
BMI				
< 30 kg/m^2	151 (70)	152 (70)	159 (74)	462 (71)
> 30 kg/m^2	64 (30)	64 (30)	57 (26)	185 (29)
Viral Load				
HCV RNA Log_{10} IU/mL	6.5 ± 0.8	6.4 ± 0.7	6.4 ± 0.8	6.4 ± 0.7
< 800,000 copies/mL	34 (15)	45 (21)	44 (20)	123 (19)
≥ 800,000 copies/mL	181 (84)	171 (79)	172 (80)	524 (81)

Characteristics	HARVONI 8 Weeks N= 215 n (%)	HARVONI + RBV 8 Weeks N = 216 n (%)	HARVONI 12 Weeks N = 216 n (%)	Total N = 647 n (%)
HCV genotype				
1a	171 (80)	172 (80)	172 (80)	515 (80)
1b	43 (20)	44 (20)	44 (20)	131 (20)
1 (no confirmed subtype)	1 (< 1)			1 (< 1)
IL28B				
CC	56 (26)	60 (28)	56 (26)	172 (27)
Non-CC	159 (74)	156 (72)	160 (74)	475 (73)
Interferon Eligible Status				
Eligible	202 (94)	203 (94)	201 (93)	606(94)

Study Results

The response rates for the treatment groups in the ION-3 trial are presented in Table 12. All treatment groups met the primary efficacy endpoint. The 8-week treatment of HARVONI without RBV was noninferior to the 8-week treatment of HARVONI with ribavirin (treatment difference 0.9%; 95% confidence interval (CI): -3.9% to 5.7%) and the 12-week treatment of HARVONI (treatment difference -1.4%; 97.5% CI: -6.4% to 3.6%). Among patients with a baseline HCV RNA <6 million IU/mL, the SVR rates were similar between 8-week and 12-week treatments of HARVONI. Among patients with a baseline HCV RNA ≥6 million IU/mL, patients treated for 8 weeks had a numerically lower SVR rate compared to those treated for 12 weeks.

Table 12. Virologic Outcome in HCV Treatment-Naïve Patients without Cirrhosis (ION-3)

	HARVONI 8 Weeks N = 215 % (n/N)	HARVONI+ RBV 8 Weeks N = 216 % (n/N)	HARVONI 12 Weeks N = 216 % (n/N)
Overall SVR12[a]	94 (202/215)	93 (201/216)	95 (206/216)
95% CI[b]	89.9 to 96.7	88.8 to 96.1	91.7 to 97.8
HCV RNA <6 million IU/mL at BL	97 (119/123)	96 (133/138)	96 (126/131)
HCV RNA ≥ 6 million IU/mL at BL	90 (83/92)	87 (68/78)	94 (80/85)
HCV RNA <LLOQ[c] by Visits			
HCV RNA < LLOQ at treatment week 4	100 (215/215)	99 (211/213)	100 (216/216)
HCV RNA < LLOQ at treatment week 12 (end of treatment)	N/A	N/A	99 (210/211)
Outcome for patients without SVR			
Overall Virologic Failure	5 (11/215)	4 (9/214)	1 (3/216)
On-Treatment Virologic Failure	0/215	0/216	0/216
Overall Relapse[d]	5 (11/215)	4 (9/214)	1 (3/216)
HCV RNA <6 million IU/mL at BL	2 (2/123)	2 (3/137)	2 (2/131)
HCV RNA ≥ 6 million IU/mL at BL	10 (9/92)	8 (6/77)	1 (1/85)
Lost to Follow Up	<1 (1/215)	2 (5/216)	2 (5/216)
Other[e]	<1 (1/215)	<1 (1/216)	1 (2/216)
Death	0	0	0
Discontinuation			
Due to AE	0	<1 (1/216)	1 (2/216)
Due to Other[f]	0	1 (2/216)	1 (3/216)

BL = baseline; N/A = not applicable

a SVR12= Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 25 IU/mL) at 12 weeks after the cessation of treatment.

b The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.

c Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected). Serum HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantitation (LLOQ) of 25 IU per mL.

d The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

e Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).

f Other includes patients who did not complete study treatment due to lost to follow up and non-compliance with study drug.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 13.

Table 13. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Naïve Patients without Cirrhosis (ION-3)

Study Outcomes	HARVONI 8-Weeks N=215 % (n/N)	HARVONI + RBV 8-Weeks N=216 % (n/N)	HARVONI 12-Weeks N=216 % (n/N)
Genotype[a]			
1a	93 (159/171)	92 (159/172)	95 (163/172)
1b	98 (42/43)	95 (42/44)	98 (43/44)
Viral Load[a] **(HCV RNA Log_{10} IU/ml)**			
< 800,000	97 (33/34)	96 (43/45)	96 (42/44)
≥ 800,000	93 (169/181)	92 (158/171)	95 (164/172)
IL28B[a]			
CC	96 (54/56)	95 (57/60)	96 (54/56)
Non-CC	93 (148/159)	92 (144/156)	95 (152/160)
BMI[a]			
< 30 Kg/m^2	93 (141/151)	91 (139/152)	95 (151/159)
≥ 30 Kg/m^2	95 (61/64)	97 (62/64)	97 (55/57)
Interferon eligible patients[a]			
Eligible	94 (190/202)	93 (188/203)	96 (192/201)

a The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, high BMI, genotype 1a, non-CC IL28B allele) had no impact on SVR12 rates.

Treatment-Naïve Patients with or without Cirrhosis [ION-1 (Study 0102)]

Trial Design

The trial design of Study ION-1 is described in Table 14.

Table 14. Summary of Trial Design in Treatment Naïve[a] Patients with or without Cirrhosis (ION-1)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, ongoing, randomized, open label, multicentre	HARVONI (90 mg/400 mg), QD, PO +/- RBV 1000 or 1200 mg/day, BID, PO	HARVONI	12 weeks
		HARVONI + RBV	12 weeks
		HARVONI	24 weeks
		HARVONI + RBV	24 weeks

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day

a. Patients were treatment naïve (defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent at the time of enrollment), with genotype 1 CHC, including those with cirrhosis. Patients were randomized in a 1:1:1:1 ratio to one of the four treatment groups and stratified by the presence or absence of cirrhosis and HCV genotype (1a vs. 1b).

Demographic and Baseline Characteristics

Demographic characteristics for patients in ION-1 are provided in Table 15.

Table 15. Demographic and Other Baseline Characteristics of HCV Treatment-Naïve Patients with or without Cirrhosis (ION-1)

Characteristics	HARVONI 12 Weeks N = 214 n (%)	HARVONI + RBV 12 Weeks N = 217 n (%)	HARVONI 24 Weeks N = 217 n (%)	HARVONI + RBV 24 Weeks N = 217 n (%)	Total N= 865 n (%)
Age (years) Mean (range)	52 (18–75)	52 (18-78)	53 (22-80)	54 (24-77)	52 (18-80)
Gender					
Male	127 (59)	128 (59)	139 (64)	119 (55)	513 (59)
Female	87 (41)	89 (41)	78 (36)	98 (45)	352 (41)
Race					
White	187 (87)	188 (87)	177 (82)	183 (84)	735 (85)
Black	24 (11)	26 (12)	32 (15)	26 (12)	108 (13)
Asian	1 (1)	0	5 (2)	5 (2)	11 (1)
Other	2 (1)	3 (1)	3 (1)	3 (1)	11 (1)
BMI					
< 30 kg/m^2	176 (82)	171 (79)	168 (77)	177 (82)	692 (80)
> 30 kg/m^2	38 (18)	46 (21)	49 (23)	40 (18)	173 (20)
Viral Load					
HCV RNA Log_{10} IU/mL	6.4 ± 0.7	6.4 ± 0.6	6.3 ± 0.7	6.3 ± 0.7	6.4 ± 0.7
< 800,000 copies/mL	45 (21)	44 (20)	49 (23)	44 (20)	182 (21)
≥ 800,000 copies/mL	169 (80)	173 (80)	168 (77)	173 (79)	683 (79)

Characteristics	HARVONI 12 Weeks N = 214 n (%)	HARVONI + RBV 12 Weeks N = 217 n (%)	HARVONI 24 Weeks N = 217 n (%)	HARVONI + RBV 24 Weeks N = 217 n (%)	Total N= 865 n (%)
HCV genotype					
1a	144 (67)	148 (68)	146 (67)	143 (66)	581 (67)
1b	66 (31)	68 (31)	68 (31)	71 (33)	273 (32)
1 (no confirmed subtype)	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	4 (< 1)
IL28B					
CC	55 (26)	76 (35)	52 (24)	73 (34)	256 (30)
Non-CC	159 (74)	141 (65)	165 (76)	144 (66)	609 (70)
Interferon Eligible Status					
Eligible	200 (93)	197 (91)	198 (91)	203 (94)	798 (92)
Cirrhosis					
Yes	34 (16)	33 (15)	33 (15)	36 (17)	136 (16)
No	178 (83)	182 (84)	184 (85)	181 (83)	726 (84)

Study Results

The response rates for the treatment groups of HARVONI with or without ribavirin for 12 weeks in the ION-1 trial are presented in Table 16. The interim primary endpoint analysis for SVR included all patients enrolled in the 12-week treatment groups (N = 431). The 12-week treatment groups met the primary efficacy endpoint. SVR rates for all patients enrolled in the 24 week treatment groups (N= 434) were not available at the time of interim analysis. However, a total of 197 patients had both posttreatment Week 12 and 24 data available for a concordance analysis (47 patients in the HARVONI 12 Week treatment group, 51 patients in the HARVONI+RBV 12 Week treatment group, 49 patients in the HARVONI 24 Week treatment group, and 50 patients in the HARVONI+RBV 24 Week treatment group). Each of the 197 patients who achieved SVR12 also achieved SVR24, resulting in a positive predictive value of 100.0% for all groups

Table 16. Virologic Outcome in HCV Adult Treatment-Naïve Patients with or without Cirrhosis (ION-1)

	HARVONI 12 Weeks N = 214 % (n/N)	HARVONI + RBV 12 Weeks N = 217 % (n/N)
SVR12[a]	98 (209/214)	97 (211/217)
95% CI[b]	94.6 to 99.2	94.1 to 99.0
HCV RNA < LLOQ[c] by visit		
HCV RNA <LLOQ[c] at treatment week 4	100 (213/213)	99 (215/217)
HCV RNA <LLOQ[c] at treatment week 12 (end of treatment for 12 week group)	100 (213/213)	100 (214/214)
Outcome for patients without SVR		
Overall Virologic Failure	<1 (1/214)	0/217
On-Treatment Virologic Failure	0/214	0/217
Relapse[d]	<1 (1/213)	0/217
Lost to Follow Up	1 (2/214)	1 (2/217)
Other[e]	1 (2/214)	1 (3/217)
Death	0	0
Discontinuation		
Due to AE	0	0
Due to Other[f]	1 (2/214)	2 (4/217)

N/A = Not Applicable

a SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ at 12 weeks (Lower Limit of Quantitation, 25 IU/mL) after the cessation of treatment.

b The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.

c Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected).

d The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

e Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).

f Other includes patients who did not complete study treatment due to lost to follow up, withdrew consent, protocol violation, lack of efficacy and pregnancy.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 17.

Table 17. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Naïve Patients with or without Cirrhosis (ION-1)

Study Outcomes	HARVONI 12-Weeks N=214 % (n/N)	HARVONI + RBV 12-Weeks N=217 % (n/N)
Genotype[a]		
1a	97 (139/144)	97 (143/148)
1b	100 (66/66)	99 (67/68)
Viral Load[a] **(HCV RNA Log_{10} IU/ml)**		
< 800,000	98 (44/45)	93 (41/44)
≥ 800,000	98 (165/169)	98 (170/173)
IL28B[a]		
CC	100 (55/55)	97 (74/76)
Non-CC	97 (154/159)	97 (137/141)
Cirrhosis		
Yes	94 (32/34)	100 (33/33)
No	98 (177/180)	97 (178/184)
BMI		
< 30 Kg/m^2	98 (172/176)	97 (166/171)
≥ 30 Kg/m^2	97 (37/38)	98 (45/46)

a The exact 95% confidence interval (CI) for the proportion within treatment group and subgroup is based on the Clopper-Pearson method. The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, cirrhosis, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates.

Treatment Experienced Patients with or without Cirrhosis [ION-2 (Study 0109)]

Trial Design

The trial design of Study ION-2 is described in Table 18.

Table 18. Summary of Trial Design in Treatment Experienced[a] Patients with or without Cirrhosis (ION-2)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	HARVONI (90 mg/400 mg), QD, PO RBV 1000 or 1200 mg/day, BID, PO	HARVONI	12 weeks
		HARVONI + RBV	12 weeks
		HARVONI	24 weeks
		HARVONI + RBV	24 weeks

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day

a Patients were treatment experienced (those who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor) genotype 1 CHC, with or without cirrhosis. Patients were randomized in a 1:1:1:1 ratio to one of the four treatment groups and stratified by the presence or absence of cirrhosis, HCV genotype (1a vs. 1b) and response to prior HCV therapy (relapse/breakthrough vs. nonresponse).

Demographics and Other Baseline Characteristics

Demographic characteristics for patients in ION-2 are provided in Table 19.

Table 19. Demographic and Other Baseline Characteristics of HCV Treatment-Experienced Patients with or without Cirrhosis (ION-2)

Characteristics	HARVONI 12 Weeks N = 109 n (%)	HARVONI + RBV 12 Weeks N = 111 n (%)	HARVONI 24 Weeks N = 109 n (%)	HARVONI + RBV 24 Weeks N = 111 n (%)	Total N = 440 n (%)
Age (years)					
Mean (range)	56 (24–67)	57 (27-75)	56 (25-68)	55 (28-70)	56 (24-75)
Gender					
Male	74 (68)	71 (64)	74 (68)	68 (61)	287 (65)
Female	35 (32)	40 (36)	35 (32)	43 (39)	153 (35)
Race					
White	84 (77)	94 (85)	91 (83)	89 (80)	358 (81)
Black	24 (22)	16 (14)	17 (16)	20 (18)	77 (18)
Asian	1 (1)	0	0	0	1 (<1)
Other	0	1 (1)	1 (1)	2 (2)	4 (1)
BMI					
< 30 kg/m^2	66 (61)	74 (67)	75 (69)	82 (74)	297 (68)
≥ 30 kg/m^2	43 (39)	37 (33)	34 (31)	29 (26)	143 (32)
Viral Load					
HCV RNA Log10 IU/mL	6.5 ± 0.4	6.4 ± 0.5	6.4 ± 0.6	6.5 ± 0.6	6.5 ± 0.5
< 800,000 copies/mL	6 (5)	13 (12)	16 (15)	15 (13)	50 (11)
≥ 800,000 copies/mL	103 (95)	98 (88)	93 (85)	96 (87)	390 (89)

Characteristics	HARVONI 12 Weeks N = 109 n (%)	HARVONI + RBV 12 Weeks N = 111 n (%)	HARVONI 24 Weeks N = 109 n (%)	HARVONI + RBV 24 Weeks N = 111 n (%)	Total N = 440 n (%)
HCV genotype					
1a	86 (79)	88 (79)	85 (78)	88 (79)	347 (79)
1b	23 (21)	23 (21)	24 (22)	23 (21)	93 (21)
IL28B					
CC	10 (9)	11 (10)	16 (15)	18 (16)	55 (13)
Non-CC	99 (91)	100 (90)	93 (85)	93 (84)	385 (88)
Cirrhosis					
Yes	22 (20)	22 (20)	22 (20)	22 (20)	88 (20)
No	87 (80)	88 (79)	86 (79)	89 (80)	350 (80)
Response to Prior HCV Treatment					
Peg-IFN +RBV	43 (39)	47 (42)	58 (53)	59 (53)	207 (47)
Relapse/ Breakthrough[a]	21 (49)	23 (49)	25 (43)	32 (54)	101 (49)
Non-Responder[b]	22 (51)	24 (51)	33 (57)	27 (49)	106 (51)
Null	17 (77)	12 (50)	19 (58)	16 (59)	64 (60)
Partial	5 (23)	12 (50)	14 (42)	11 (41)	42 (40)
PI+ Peg-IFN +RBV	66 (61)	64 (58)	50 (46)	51 (46)	231 (53)
Relapse/ Breakthrough[a]	39 (59)	42 (66)	35 (70)	28 (55)	144 (62)
Non-Responder[b]	27 (41)	22 (34)	15 (30)	23 (45)	87 (38)

b Relapse/Breakthrough: Patient achieved undetectable HCV RNA levels (HCV RNA < LLOQ) during treatment or within 4 weeks of the end of treatment, but did not achieve SVR.

c Non-Responder: Patient did not achieve undetectable HCV RNA levels (HCV RNA ≥ LLOQ) while on treatment.

Study Results

The response rates for the treatment groups in study ION-2 are presented in Table 20. All treatment groups met the primary efficacy endpoint. A total of 98 patients in the HARVONI 12 Week treatment arm and 107 patients in the HARVONI+RBV 12 Week treatment arm had both posttreatment Week 12 and 24 data available for a concordance analysis. Each of the 205 patients who achieved SVR12 also achieved SVR24, resulting in a positive predictive value of 100.0% in both groups.

Table 20. Virologic Outcome in Treatment-Experienced HCV Patients with or without Cirrhosis (ION-2)

	HARVONI 12 Weeks N=109 % (n/N)	HARVONI +RBV 12 Weeks N=111 % (n/N)	HARVONI 24 Weeks N=109 % (n/N)	HARVONI +RBV 24 Weeks N=111 % (n/N)
SVR12[a]	94 (102/109)	96 (107/111)	99 (108/109)	99 (110/111)
95% CI[b]	87.2 to 97.4	91.0 to 99.0	95.0 to 100.0	95.1 to 100.0
SVR24[c]	94 (102/109)	96 (107/111)	99 (108/109)	99 (110/111)
HCV RNA <LLOQ[d] by Visit				
HCV RNA <LLOQ[d] at treatment week 4	100 (109/109)	99 (110/111)	99 (108/109)	99 (110/111)
HCV RNA <LLOQ[d] at treatment week 12 (end of treatment for 12 week group)	99 (108/109)[e]	100 (111/111)	100 (109/109)	100 (110/110)
HCV RNA <LLOQ[d] at treatment week 24 (end of treatment)	N/A	N/A	100 (107/107)	100 (110/110)
Outcome for patients without SVR				
Overall Virologic Failure	6 (7/109)	4 (4/111)	0/109	1 (1/111)
On-Treatment Virologic Failure	0/109	0/111	0/109	1 (1/111)[f]
Relapse[g]	6 (7/108)	4 (4/111)	0/109	0/110
Lost to Follow Up	0/109	0/111	0/109	0/111
Other[h]	0/109	0/111	1 (1/109)	0/111
Death	0	0	0	0
Discontinuation				
Due to AE	0	0	0	0
Due to Other[i]	0	0	2 (2/109)	1 (1/111)

N/A = not available

a SVR12, Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 25 IU/mL) at 12 weeks after the cessation of treatment.

b The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.

c SVR24, defined as HCV RNA less than LLOQ (25 IU/mL) at 24 weeks after cessation of treatment.

d Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected).

e The one patient who did not achieve HCV RNA <LLOQ at the last on treatment visit achieved SVR12.

f This patient was discontinued after 6 weeks of treatment due to lack of efficacy (rebound) and never achieved HCV RNA <LLOQ. Plasma concentrations of GS-331007 and LDV at weeks 2, 4 and 6 were indicative of noncompliance with the study drug at or around these study visits.

g The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

h Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).

i Other includes patients who did not complete study treatment due to protocol violation and lack of efficacy.

Response rates for selected subgroups are presented in Table 21.

Table 21. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Experienced Patients with or without Cirrhosis (ION-2)

Study Outcomes	HARVONI 12 Weeks N=109 % (n/N)	HARVONI +RBV 12 Weeks N=111 % (n/N)	HARVONI 24 Weeks N=109 % (n/N)	HARVONI +RBV 24 Weeks N=111 % (n/N)
Genotype[a]				
1a	95 (82/86)	95 (84/88)	99 (84/85)	99 (87/88)
1b	87 (20/23)	100 (23/23)	100 (24/24)	100 (23/23)
Viral Load[a] **(HCV RNA Log_{10} IU/ml)**				
< 800,000	83 (5/6)	100 (13/13)	100 (16/16)	100 (15/15)
≥ 800,000	94 (97/103)	96 (94/98)	99 (92/93)	99 (95/96)
Cirrhosis[a]				
Yes	86 (19/22)	82 (18/22)	100 (22/22)	100 (22/22)
No	95 (83/87)	100 (89/89)	99 (86/87)	99 (88/89)
IL28B[a]				
CC	100 (10/10)	100 (11/11)	100 (16/16)	94 (17/18)
Non-CC	93 (92/99)	96 (96/100)	99 (92/93)	100 (93/93)
BMI[a]				
< 30 Kg/m^2	92 (61/66)	96 (71/74)	99 (74/75)	99 (81/82)
≥ 30 Kg/m^2	95 (41/43)	97 (36/37)	100 (34/34)	100 (29/29)
Response to Prior HCV Therapy[a]				
Relapse/ Breakthrough	95 (57/60)	97 (63/65)	100 (60/60)	98 (59/60)
Non-Responder	92 (45/49)	96 (44/46)	98 (48/49)	100 (51/51)
Prior HCV Therapy[a]				
PI + PEG-IFN + RBV	94 (62/66)	97 (62/64)	98 (49/50)	100 (51/51)
PEG-IFN + RBV	93 (40/43)	96 (45/47)	100 (58/58)	98 (58/59)
Cirrhosis by Prior HCV Therapy[a]				
PI + PEG-IFN + RBV				
Yes	86 (12/14)	85 (11/13)	100 (14/14)	100 (13/13)
No	96 (50/52)	100 (51/51)	97 (35/36)	100 (38/38)
PEG-IFN + RBV				
Yes	88 (7/8)	78 (7/9)	100 (8/8)	100 (9/9)
No	94 (33/35)	100 (38/38)	100 (50/50)	98 (49/50)

a The exact 95% confidence interval (CI) for the proportion within treatment group and subgroup is based on the Clopper-Pearson method. The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates. Treatment-experienced patients with cirrhosis who received 12 weeks of treatment showed numerically lower SVR rates compared with treatment-experienced patients with cirrhosis who received 24 weeks of treatment (±RBV).

Previously-Treated Patients with Compensated Cirrhosis [SIRIUS (Study 0121)]

SIRIUS was a randomized, double-blind and placebo-controlled trial that evaluated the efficacy of HARVONI+RBV for 12 weeks or HARVONI without RBV for 24 weeks in genotype 1 CHC patients with compensated cirrhosis who failed prior therapy with a Peg–IFN+RBV regimen followed by a subsequent failure with a protease inhibitor (PI)-based regimen (Peg-IFN+RBV+ an HCV PI) . Patients were randomized in a 1:1 ratio to receive HARVONI for 24 weeks or placebo for 12 weeks followed by HARVONI+RBV for 12 weeks. Randomization was stratified by HCV genotype (1a vs 1b) and response to prior HCV therapy (never achieved HCV RNA less than LLOQ vs achieved HCV RNA less than LLOQ).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 155 randomized patients, the median age was 56 years (range: 23 to 77); 74% of the patients were male; 97% were White; mean body mass index was 27 kg/m^2 (range: 19 to 47 kg/m^2); 63% had genotype 1a HCV infection; 94% had non-C/C IL28B alleles (CT or TT). All patients (with the exception of 1) met the protocol defined definition of cirrhosis as defined by biopsy, transient elastography (>12.5 kPa) or FibroTest score >0.75 and an AST: platelet ratio index (APRI) >2. One patient discontinued therapy while on placebo, and was not included in the efficacy analysis.

The SVR was 96% (74/77, 95% CI: 89.0% to 99.2%) and 97% (75/77, 95% CI: 90.9% to 99.7%) in patients treated with HARVONI+RBV for 12 weeks and HARVONI for 24 weeks without RBV, respectively.

All 5 patients who did not achieve SVR12 relapsed.

Patients with Other HCV Genotypes

Genotype 2

In a Phase 2 open-label trial (LEPTON), the safety and efficacy of HARVONI were evaluated in 26 treatment-naïve or treatment-experienced patients with genotype 2 HCV infection, with or without cirrhosis. The SVR12 rate was 96% (25/26). Two patients had cirrhosis and both achieved SVR. The patient who did not achieve SVR12 withdrew consent and discontinued from the study after receiving a single dose of HARVONI.

Genotype 3

In a Phase 2 open-label trial, the safety and efficacy of HARVONI were evaluated with or without RBV in 51 treatment-naïve patients and 50 treatment-experienced patients, with genotype 3 HCV infection, with or without cirrhosis. Treatment-naïve patients were treated with HARVONI (N=25) or HARVONI + RBV (N=26) for 12 weeks. All treatment-experienced

patients were treated with HARVONI + RBV for 12 weeks. SVR12 rates in treatment-naïve patients were 64% (16/25) and 100% (26/26) in the HARVONI and HARVONI + RBV treatment groups, respectively. SVR12 rates in treatment-naïve patients with cirrhosis were 25% (1/4) and 100% (6/6) in the HARVONI and HARVONI + RBV treatment groups, respectively. The SVR12 rate in treatment-experienced patients was 82% (41/50).The SVR12 rate in treatment-experienced patients with cirrhosis was 73% (16/22). Eight patients relapsed and one patient experienced on-treatment virologic failure. The safety of HARVONI with or without RBV was comparable to that observed in patients with genotype 1 HCV infection treated with HARVONI with or without RBV in Phase 3 clinical trials.

Genotype 4

In two open-label studies (Study 1119 and ION-4), HARVONI was administered for 12 weeks to treatment-naïve or treatment-experienced patients with genotype 4 CHC, with or without cirrhosis. Study 1119 enrolled 44 treatment-naïve or treatment-experienced patients with genotype 4 CHC, with or without cirrhosis. Study ION-4 enrolled 8 treatment-naïve or treatment-experienced patients with genotype 4 CHC who are co-infected with HIV-1, none of whom had cirrhosis.

In Study 1119, the SVR12 was 93% (95% [21/22] in treatment-naïve patients and 91% [20/22] in treatment-experienced patients). All 3 patients who failed to achieve SVR12 relapsed; SVR12 was 100% in the 10 patients with cirrhosis. In Study ION-4, 100% (8/8) patients achieved SVR12.

Genotype 5

In the open-label Study 1119, HARVONI was administered for 12 weeks to 41 treatment-naive or treatment-experienced patients with genotype 5 CHC, with or without cirrhosis.

The SVR12 rate was 93% (90% [19/21] in treatment-naïve patients and 95% [19/20] in treatment-experienced patients). The SVR12 was 89% (8/9) in patients with cirrhosis. Of the 3 patients who failed to achieve SVR12, 2 patients relapsed and one patient was lost to follow-up.

Genotype 6

In the open-label Study ELECTRON-2, HARVONI was administered for 12 weeks to 25 treatment-naive or treatment-experienced patients with genotype 6 CHC, with or without cirrhosis. The SVR12 rate was 96% (24/25). Two patients had cirrhosis and both achieved SVR.

The single patient who relapsed discontinued study treatment early (at approximately Week 8 of 12).

Clinical Trials in Patients with HCV/HIV-1 Co-infection

ION-4 was an open-label clinical trial that evaluated the safety and efficacy of 12 weeks of treatment with HARVONI without RBV in HCV treatment-naïve and treatment-experienced patients with genotype 1 or 4 CHC who were co-infected with HIV-1. Treatment-experienced

patients had failed prior treatment with Peg-IFN+RBV, Peg-IFN+RBV+ an HCV protease inhibitor or SOVALDI+RBV± Peg-IFN. Patients were on a stable HIV-1 antiretroviral therapy that included emtricitabine + tenofovir disoproxil fumarate (TDF), administered with efavirenz, rilpivirine or raltegravir.

Of the 335 treated patients, the mean age was 52 years (range: 26 to 72); 82% of the patients were male; 18% were female; 61% were White; 34% were Black; 5% were classified as "Other" race; mean body mass index was 27 kg/m^2 (range: 18 to 66 kg/m^2); 75%, 23% and 2% had genotype 1a, 1b and 4 HCV infection, respectively; 76% had non-C/C IL28B alleles (CT or TT); 24% had the CC IL28B allele; 89% had a viral load ≥ 800, 000 IU/mL; and 20% had compensated cirrhosis. Fifty-five percent (55%) of the patients were treatment-experienced.

Table 22 presents the response rates in the ION-4 trial after 12 weeks of HARVONI treatment.

Table 22 Virologic Outcome in Patients with HCV/HIV-1 Co-infection (ION-4)

	HARVONI 12 Weeks Genotype 1 N = 327 (%)	**HARVONI 12 Weeks Genotype 4 N = 8 (%)**
SVR	313 (96)	8 (100)
Outcome for patients without SVR		
On-Treatment Virologic Failure	2 (<1)	0
Relapse[a]	10 (3)	0
Other[b]	2 (<1)	0
Cirrhosis		
Yes	250/260 (96)	0
No	63/67 (94)	8/8 (100)
Prior HCV Treatment		
Treatment-Naïve	138/146 (95)	4/4 (100)
Treatment-Experienced	175/181 (97)	4/4 (100)
Treatment-Experienced patients with cirrhosis	46/47 (98)	0

a The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b Other includes patients who did not achieve SVR and did not meet virologic failure criteria (eg, lost to follow-up).

No patient had HIV-1 rebound during the study and no clinically meaningful changes in CD4+ cell count from baseline were observed.

The relapse rate in the ION-4 trial in Black patients was 9% (10/115), all of whom were IL28B non-CC genotype, and none in non-Black patients (0/220). In the ION-1, ION-2, and ION-3 HCV mono-infection studies, relapse rates were 3% (10/305) in Black patients and 2% (26/1637) in non-Black patients.

Clinical Trials in Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

SOLAR-1 and SOLAR-2 were two open-label clinical trials that evaluated 12 and 24 weeks of treatment with HARVONI in combination with RBV in genotype 1 and 4 CHC patients who have undergone liver transplantation and/or who have decompensated liver disease. The two trials were identical in study design and were pooled for analysis. Patients were enrolled in one of the seven groups based on liver transplantation status and severity of hepatic impairment (see Table 23) (Cohort A, Patients without a liver transplant; and Cohort B, Posttransplantation). Patients with a Child-Pugh-Turcotte (CPT) score >12 were excluded. Within each group, patients were randomized in a 1:1 ratio to receive HARVONI + RBV for 12 weeks or HARVONI+RBV for 24 weeks.

Demographics and baseline characteristics were balanced across the treatment groups. Of the 670 treated patients, the mean age was 58 years (range: 21 to 81); 77% of the patients were male; 23% were female; 91% were White; 5% were Black; 3% were classified as "Other" race; mean body mass index was 28 kg/m^2 (range: 18 to 49 kg/m^2); 60%, 34% and 6% had genotype 1a, 1b, and 4 HCV infection, respectively; 81% had non-C/C IL28B alleles (CT or TT); 19% had the IL28B CC allele; 78% of the patients failed a prior HCV therapy. Among the patients who had decompensated cirrhosis (pre- or post-transplant), 64% and 36% were CPT class B and C at screening, respectively and 24% had a baseline Model for End Stage Liver Disease (MELD) score greater than 15.

Table 23 presents the SVR rates in patients with genotype 1 CHC (pooled results for SOLAR-1 and SOLAR-2). Overall, 92.7% (569 of 614) patients with genotype 1 CHC achieved the primary endpoint, SVR12.

No patients experienced on-treatment virologic failure. Of the 45 genotype 1 patients who did not achieve SVR12, 20 relapsed, 22 died, and 3 could not be assessed for SVR12 due to withdrawal of consent (n=2) or never had HCV RNA < LLOQ prior to obtaining a posttreatment Week 12 HCV RNA result (n=1).

Table 23 Sustained Virologic Response and Relapse Rates in Genotype 1 CHC patients (pooled SOLAR-1 and SOLAR-2)[a, b, c]

	HARVONI+RBV 12 weeks N=307[d, e]		HARVONI+RBV 24 weeks N=307[d, e]	
	SVR12 (%[n/N])	Relapse (%[n/N])	SVR12 (%[n/N])	Relapse (%[n/N])
Pretransplant[f] (Cohort A)				
CPT B (Group 1)	87% (45/52)	12% (6/51)	92% (46/50)	4% (2/48)
CPT C (Group 2)	88% (35/40)	5% (2/37)	83% (38/46)	7% (3/41)
Posttransplant[g] (Cohort B)				
Metavir score F0-F3 (Group 3)	95% (94/99)	3% (3/97)	99% (99/100)	0/99
CPT A (Group 4)	98% (55/56)	0/55	96% (51/53)	0/51
CPT B (Group 5)	89% (41/46)	2% (1/42)	96% (43/45)	0/43

	HARVONI+RBV 12 weeks N=307[d, e]		HARVONI+RBV 24 weeks N=307[d, e]	
CPT C (Group 6)	57% (4/7)	33% (2/6)	78% (7/9)	13% (1/8)
Fibrosing cholestatic hepatitis (Group 7)	100% (7/7)	0/7	100% (4/4)	0/4

a- Deaths and those patients with "other" virologic outcome were considered treatment failures. For relapse rates, deaths and those patients with 'Other' virologic outcome (ie, who did not achieve SVR12 or meet virologic failure criteria) are excluded from the analysis.
b- Relapse to posttreatment Week 12 = confirmed HCV RNA ≥ LLOQ during the posttreatment period up to posttreatment Day 146 having achieved HCV RNA < LLOQ at last on-treatment visit.
c- Patients who did not achieve SVR12 and did not have virologic failure prior to posttreatment Day 146; and patients transplanted while on treatment or prior to posttreatment Day 70 with HCV RNA < LLOQ at last HCV RNA prior to transplant were excluded from analysis.
d- Twelve patients transplanted prior to post-treatment Week 12 with HCV RNA<LLOQ at last measurement prior to transplant were excluded.
e- Two patients who did not have decompensated cirrhosis and had also not received a liver transplant were excluded due to failure to meet the inclusion criteria for any of the treatment groups.
f- Pretransplantation means patients who have never undergone transplantation and includes those who are on the waitlist to receive liver transplant (were expected to be at least 12 weeks from transplantation).
g- Posttransplantation includes patients who have undergone at least one liver transplant

In genotype 4 CHC post-liver transplant patients without cirrhosis or with compensated cirrhosis treated for 12 weeks (N=12) or 24 weeks (N=10), respectively, the SVR12 rates were similar to that seen to rates reported with genotype 1 CHC. No patients relapsed. There is limited data in patients with genotype 4 CHC and decompensated cirrhosis (pre- and post-liver transplantation). Therefore, the safety and efficacy in patients with genotype 4 CHC and decompensated cirrhosis (pre- and post-liver transplantation) could not be established.

A total of 123 patients with HCV and decompensated cirrhosis (pre- or post-transplant), who achieved SVR12 and had post-treatment Week 12 laboratory data available, were assessed for changes from baseline in their MELD and CPT scores.

Change in MELD score: 57% (70/123) and 19% (23/123) had an improvement or no change in MELD score from baseline to post-treatment week 12, respectively; of the 32 patients whose MELD score was ≥ 15 at baseline, 59% (19/32) had a MELD score < 15 at post-treatment Week 12. Improvement in MELD scores was driven largely by improvement in bilirubin.

Change in CPT: 60% (74/123) and 34% (42/123) had an improvement or no change of CPT scores from baseline to post-treatment week 12, respectively; of the 32 patients who had CPT C cirrhosis at baseline, 53% (17/32) had CPT B cirrhosis at post-treatment Week 12; of the 88 patients who had CPT B cirrhosis at baseline, 25% (22/88) had CPT A cirrhosis at post-treatment Week 12. Improvement in CPT scores was driven largely by improvement in bilirubin.

Pediatrics (12 to < 18 years of age)

The efficacy of HARVONI in HCV infected patients 12 to <18 years of age was evaluated in a Phase 2, open label clinical trial that enrolled 100 patients with genotype 1 CHC. A total of 80 patients (80%) were treatment-naïve and 20 patients (20%) were treatment-experienced. All patients in the trial were treated with HARVONI for 12 weeks.

Demographics and baseline characteristics were balanced across treatment-naïve and treatment-experienced patients. Of the 100 treated patients, the median age was 15 years (range: 12 to 17); 63% of the patients were female; 90% were White, 7% were Black, and 2% were Asian; 13% were Hispanic/Latino; mean body mass index was 23 kg/m^2 (range: 13.1 to 36.6 kg/m^2); 55% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 81% had genotype 1a HCV infection; 76% had non-CC IL28B alleles (CT or TT); 1 patient had known compensated cirrhosis. The majority of patients (84%) had been infected through vertical transmission.

The SVR12 rate was 98% overall (98% [78/80] in treatment-naïve patients and 100% [20/20] in treatment-experienced patients). No patient experienced on-treatment virologic failure or relapse. Two out of 100 patients were lost to follow-up.

DETAILED PHARMACOLOGY

Pharmacodynamics

Effect on Electrocardiogram

Thorough QT studies have been conducted for ledipasvir and sofosbuvir.

The effect of ledipasvir 120 mg twice daily for 10 days on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) three period crossover thorough QT trial in 59 healthy subjects. The effects of sofosbuvir at the therapeutic dose (400 mg) and 3-fold above therapeutic dose (1200 mg) on QTc interval were evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects.

The results from both studies showed the expected effect of the single dose of moxifloxacin (positive control) on the QTc interval, indicating that the study had appropriate assay sensitivity; the lower bound of the 2 sided 90% confidence interval was > 5 msec at more than 1 time point.

Evaluation of the baseline-adjusted mean differences between ledipasvir 120 mg BID, sofosbuvir 400 mg or 1200-mg doses and placebo and their associated 2-sided 90% confidence intervals demonstrated a lack of effect of ledipasvir or sofosbuvir on prolongation of the QTcF interval (primary PD endpoint). The upper bounds of the 90% confidence intervals were < 10 msec at all time points after dosing. Consistent with the results using the QTcF correction formula, the upper bounds of the 2-sided 90% confidence intervals were < 10 msec for ledipasvir and both doses of sofosbuvir at all time points using other correction methods.

Ledipasvir AUC_{0-24} and C_{max} were 3.7- fold and 4.2-fold higher, respectively, than the mean exposure (based on population PK exposures) achieved in Phase 2 and 3 studies following administration of HARVONI. The mean exposures of GS-331007 (AUC_{0-24} and C_{max}) and sofosbuvir (AUC_{0-24} and C_{max}) at the supratherapeutic dose (sofosbuvir 1200 mg) were approximately 2.2-, 2.9-, 1.8-, and 3.4-fold higher, respectively, than the mean exposures (based on population PK exposures) achieved following administration of HARVONI.

Safety Pharmacology

The effects of ledipasvir on the central nervous, cardiovascular and respiratory systems were examined in a core battery of safety pharmacology studies. The studies did not reveal any concerns for cardiovascular, respiratory, or CNS effects.

The effects of sofosbuvir (evaluated as GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer) on the central nervous, cardiovascular, and respiratory systems were examined in a core battery of safety pharmacology studies. The studies presented have not identified any undesirable pharmacodynamic effect of sofosbuvir on physiological function at therapeutic dose level.

Pharmacokinetics

Ledipasvir AUC is dose proportional over the dose range of 3 to 100 mg. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg.

Based on the population pharmacokinetic analysis in HCV-infected patients, geometric mean steady-state AUC_{0-24} for ledipasvir (N=2113), sofosbuvir (N=1542), and GS-331007 (N=2113) were 7290, 1320 and 12,000 ng•hr/mL, respectively. Steady-state C_{max} for ledipasvir, sofosbuvir and GS-331007 were 323, 618 and 707 ng/mL, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and subjects with HCV infection. Relative to healthy subjects (N=191), ledipasvir AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively in HCV-infected subjects.

Absorption

The pharmacokinetic properties of ledipasvir, sofosbuvir, and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Following oral administration of HARVONI, ledipasvir median peak concentrations were observed 4.0 to 4.5 hours post-dose. Sofosbuvir was absorbed quickly and the peak median plasma concentration was observed ~ 0.8 to 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed between 3.5 to 4 hours post-dose.

Effects of Food

The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without food.

A study conducted in 28 healthy subjects showed that relative to fasting conditions, for GS-331007, an approximately 18% to 30% lower C_{max} was observed upon administration of HARVONI with food, with no change in AUC (90% CIs of the Geometric Mean Ratios (GMRs) were contained within 80-125%). The decrease in GS-331007 C_{max} was not considered clinically significant. Similar LDV plasma exposures (AUC and C_{max}) were achieved upon administration of HARVONI under fasted or fed conditions (90% CIs of the GMRs were contained within 70-143%).

The administration of a single dose of HARVONI with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal slowed the rate of absorption of SOF (high or moderate fat meal versus fasted; prolonged T_{max}: 2.0-2.25 hours versus 1.0 hours) but did not substantially affect the sofosbuvir C_{max} and AUC_{inf} as evidenced by < 30% higher C_{max} and < 2-fold higher mean AUC.

HARVONI can be administered without regard to food.

Distribution

Ledipasvir is >99.8% bound to human plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. After a single 90 mg dose of [^{14}C]-ledipasvir in 8 healthy adult male subjects, the blood to plasma ratio of ^{14}C-radioactivity ranged between 0.51 and 0.66, indicating that total radioactivity was excluded from erythrocytes. [^{14}C]-ledipasvir-derived radioactivity was absorbed and widely distributed to tissues (eg, alimentary canal, liver, kidney, pancreas, adrenal gland, and brown fat) of male mice and rats after a single oral dose. Low levels of [^{14}C]-ledipasvir-derived radioactivity were observed in the CNS, bone, eye and testes. Plasma LDV exposure in nursing pups of postpartum female rats orally administered LDV illustrates transfer into milk.

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal (< 10%) in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy male subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

After a single 400 mg dose of [^{14}C]-sofosbuvir in 7 healthy adult male subjects, derived radioactivity was absorbed and widely distributed to tissues (eg, alimentary canal, lymphatic system, excretory system) of male rats and pregnant, non-pregnant, and postpartum female rats after a single oral dose. Drug-derived radioactivity was transferred through the placenta of females and was found in amniotic fluid and absorbed into fetuses. Low levels of [^{14}C]-sofosbuvir-derived radioactivity were observed in the CNS, bone, eye, testes, and white adipose. Fetal blood and brain levels of drug-related material were higher than those observed in dams. Levels of drug-derived radioactivity were quantifiable in the milk collected from postpartum females. Levels of drug-derived radioactivity were transferred into nursing pups and were detectable in the liver and gastrointestinal (GI)/stomach contents. See **WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women.**

Metabolism

In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP 2C19, CYP2D6, and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90 mg [^{14}C]-ledipasvir to 8 healthy adult male subjects, the systemic exposure was almost exclusively due to the parent drug (> 98%) with 1.1% and 0.75% attributed to unidentified metabolites (M1 and M12, respectively).

Unchanged ledipasvir is the major species present in feces.

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*.

In a human mass balance study conducted with sofosbuvir administered as a single agent at a 400 mg oral dose of [^{14}C]-sofosbuvir in healthy male subjects (n=7), sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

Excretion

Following a single 90 mg oral dose of [^{14}C]-ledipasvir to 8 healthy adult male subjects, the mean cumulative urinary and fecal recovery of the [^{14}C]-radioactivity was approximately 87%, with most of the radioactive dose recovered in the feces (approximately 86%). The major component excreted in feces was unchanged ledipasvir, accounting for a mean of 70% of the administered dose; the oxidative metabolite M19 accounted for 2.2% of the dose. These data suggest that biliary excretion of unchanged ledipasvir is a major route of elimination with renal excretion being a minor pathway (approximately 1%). The median terminal half-life of ledipasvir following administration of HARVONI was 47 hours.

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir in healthy male subjects (n=7), mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. Renal clearance is the major elimination pathway for GS-331007. Consistent with substantial elimination of GS-331007 in the urine, clinically significant changes in GS-331007 PK were noted with declining renal function. The median terminal half-life of sofosbuvir and GS-331007 following administration of HARVONI were 0.5 and 27 hours respectively.

Special Populations and Conditions

Hepatic Insufficiency

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Safety and efficacy of HARVONI have been established in adult patients with decompensated cirrhosis (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of ledipasvir was studied with a single dose of 90 mg ledipasvir in 10 HCV negative subjects with normal hepatic function and 10 HCV negative matched control

subjects with severe hepatic impairment (Child Pugh Class C). Similar AUC_{inf}, a modestly lower (approximately 35%) C_{max} and prolonged terminal $t_{1/2}$ (median 84.25 hrs vs 45.72 hrs) observed in subjects with severe hepatic impairment as compared to subjects with normal hepatic function. A reduction in C_{max} in the absence of a change in AUC was not deemed clinically important. Mild and moderate hepatic impairment is not expected to meaningfully alter the pharmacokinetics of ledipasvir. No dose adjustment of ledipasvir is recommended for patients with mild, moderate, or severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of ledipasvir (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Mild hepatic impairment is not expected to meaningfully alter the pharmacokinetics of sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate, or severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007 (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency

Renal impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in patients with mild or moderate renal impairment. The safety of HARVONI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or ESRD requiring hemodialysis (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in 10 HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault) and 10 matched control subjects with normal renal function (eGFR ≥ 90 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment. An evaluation of lediapasvir pharmacokinetics in subjects with ESRD has not been conducted. No dose adjustment of ledipasvir is required for patients with mild, moderate, or severe renal impairment.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects with end stage renal disease (ESRD) requiring hemodialysis following a single 400 mg dose of sofosbuvir (N=6/group). Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir AUC_{inf} was 61%, 107% and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 AUC_{inf} was 55%, 88% and 451% higher, respectively. In subjects with ESRD,

sofosbuvir AUC_{inf} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis. The AUC_{inf} of GS-331007 in subjects with ESRD administered sofosbuvir 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively, compared to normal subjects.

Hemodialysis is required for the elimination of GS-331007 (extraction ratio 53%) in subjects with ESRD; following a single 400 mg dose of sofosbuvir, a 4 hour hemodialysis removed approximately 18% of administered dose. No dose adjustment of sofosbuvir is required for patients with mild or moderate renal impairment. The safety of HARVONI has not been assessed in patients with severe renal impairment or ESRD (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions

As HARVONI contains ledipasvir and sofosbuvir, any interactions that have been identified with these agents individually may occur with HARVONI.

Potential for HARVONI to Affect Other Drugs

Ledipasvir is an inhibitor of intestinal efflux drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir is an inhibitor of hepatic uptake transporters OATP1B1, OATP1B3, and hepatic efflux transporter BSEP only at concentrations exceeding those achieved in clinic. Ledipasvir is not an inhibitor of renal efflux transporters MRP2, MRP4, MATE1, renal uptake transporters OCT2, OAT1, OAT3, and hepatic uptake transporter OCT1. The drug-drug interaction potential of ledipasvir is primarily limited to the process of intestinal absorption. Clinically relevant transporter inhibition by ledipasvir in the systemic circulation is not expected due to its high protein binding. Sofosbuvir and GS-331007 are not inhibitors of efflux transporters drug transporters P-gp, BCRP, renal efflux transporter MRP2, hepatic efflux transporter BSEP, hepatic uptake transporters OATP1B1, OATP1B3, and OCT1 and GS-331007 is not an inhibitor of renal uptake transporters OAT1, OCT2, and renal efflux transporter MATE1.

Ledipasvir inhibits UGT1A1 only at concentrations exceeding those achieved in the clinic. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Potential for Other Drugs to Affect HARVONI

Ledipasvir and sofosbuvir are substrates of efflux drug transporters P-gp and BCRP while GS-331007 is not. Drugs that are potent P-gp inducers (eg, rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of HARVONI and should not be used with HARVONI (see **WARNINGS AND PRECAUTIONS, Use with Potent P-gp Inducers**). Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir and ledipasvir plasma concentrations without increasing GS-331007 plasma concentration; HARVONI may be coadministered with P-gp and/or BCRP inhibitors. Neither ledipasvir nor sofosbuvir is a substrate for hepatic uptake

transporters OCT1, OATP1B1, or OATP1B3. GS-331007 is not a substrate for renal transporters including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2.

Ledipasvir is subject to slow oxidative metabolism via an unknown mechanism. *In vitro*, no detectable metabolism of ledipasvir by CYP enzymes has been observed. Biliary excretion of unchanged ledipasvir is a major route of elimination. Sofosbuvir is not a substrate for CYP and UGT1A1 enzymes. Clinically significant drug interactions with HARVONI mediated by CYP or UGT1A1 enzymes are not expected.

Based on these data, ledipasvir, sofosbuvir and its metabolites are predicted to have low liability to cause clinically significant drug interactions through human CYP or drug transporters. The fact that ledipasvir and sofosbuvir are substrates of P-gp and BCRP suggests that they may be susceptible to modest changes in PK that can occur via P-gp and/or BCRP transporter-based drug interactions. Clinical studies were conducted to evaluate the effect of drugs that can affect or be affected by ledipasvir, sofosbuvir, and GS-331007 during co-administration (see **DRUG INTERACTIONS**).

MICROBIOLOGY

Antiviral Activity in Cell Culture

In HCV replicon assays, the EC_{50} values of ledipasvir against full-length replicons from genotype 1a and 1b were 0.031 nM and 0.004 nM, respectively. The median EC_{50} of ledipasvir against chimeric replicons encoding NS5A sequences from clinical isolates was 0.018 nM for genotype 1a (range 0.009-0.085 nM; N=30) and 0.006 nM for genotype 1b (range 0.004-0.007 μM; N=3). Ledipasvir has EC_{50} values of 21 nM in genotype 2a and 16 nM against the genotype 2b replicons that have leucine at amino acid position 31 (L31) in NS5A, but has a significantly reduced activity against the genotype 2a replicon (EC_{50} = 249 nM) and the genotype 2b replicon (EC_{50} = 530 nM) that both have methionine at position 31 (M31) as well as genotype 3 replicons (EC_{50} = 168 nM). In addition, ledipasvir is active against genotypes 4a, 5a, and 6a, with EC_{50} values of 0.39 nM, 0.15 nM, and 1.1 nM, respectively. Ledipasvir has substantially lower activity against genotypes 2a, 2b, 3a, and 6e with EC_{50} values of 21-249 nM, 168 nM, and 264 nM, respectively. The presence of 40% human serum reduced anti-HCV activity of ledipasvir by 12-fold against genotype 1a HCV replicon.

Sofosbuvir exhibits pan-genotypic anti-HCV activity. In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a, and 4a, and chimeric 1b replicons encoding NS5B from genotype 2b, 5a, or 6a ranged from 14 to 110 nM. The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 62 nM for genotype 1a (range 29-128 nM; N=67), 102 nM for genotype 1b (range 45-170 nM; N=29), 29 nM for genotype 2 (range 14-81 nM; N=15), and 81nM for genotype 3a (range 24-181 nM; N=106). In infectious virus assays, the EC_{50} values of sofosbuvir against genotype 1a and 2a were 30 and 20 nM, respectively. The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.

Since there is about 65% homology of the HCV NS5B polymerase across HCV genotypes, and since GS-461203 binds to a highly conserved region of RdRp, sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B polymerase with a high barrier to resistance. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC50 value ranging from 0.7 to 2.6 μM. GS-461203 is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Evaluation of sofosbuvir in combination with ledipasvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Antiviral Activity *in vivo*

In patients taking HARVONI, an average HCV RNA viral load decline of -4.5 (log_{10} IU/ml) was observed by Week 1 of treatment.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to ledipasvir have been selected in cell culture for genotype 1a and 1b. Reduced susceptibility to ledipasvir was associated with the primary NS5A substitution Y93H in both genotype 1a and 1b. Additionally a Q30E substitution emerged in genotype 1a replicons. Site-directed mutagenesis of the Y93H in both genotype 1a and 1b as well as the Q30E substitution in genotype 1a conferred high levels of reduced susceptibility to ledipasvir (fold change in EC_{50} greater than 1000-fold).

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a, and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a, and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In Clinical Trials

Genotype 1

In a pooled analysis of patients who received HARVONI in Phase 3 trials (ION-3, ION-1, and ION-2), 37 (2.3%) patients (29 with genotype 1a and 8 with genotype 1b) qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA > 1000 IU/ml. Post-baseline NS5A and NS5B deep sequencing data (assay cutoff of 1%) were available for 37/37 and 36/37 patients, respectively.

NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 29/37 patients not achieving SVR. Of the 29 genotype 1a patients who qualified for resistance testing,

22/29 (76%) patients harbored one or more NS5A RAVs at positions K24, M28, Q30, L31, S38, and Y93 at failure, while the remaining 7/29 patients had no NS5A RAVs detected at failure. The most common variants were Q30R (36.4%), Y93H (27.3%) L31M (22.7%), Y93N (18.2%), Q30H (13.6%), and M28T (9.1%). Of the 8 genotype 1b patients who qualified for resistance testing, 7/8 (88%) harbored one or more NS5A RAVs at positions L31 and Y93 at failure, while 1/8 patients had no NS5A RAVs at failure. The most common variant was Y93H (85.7%). Among the 8 patients who had no NS5A RAVs at failure, 7 patients received 8 weeks of treatment (N=3 with HARVONI; N=4 with HARVONI + RBV) and 1 patient received HARVONI for 12 weeks. In phenotypic analyses, post-baseline isolates from patients who harbored NS5A RAVs at failure showed 20- to >243-fold reduced susceptibility to ledipasvir.

There were 24 virologic failures (20 relapses and 4 discontinuation prior to achieving HCV RNA <LLOQ). Among post-transplant patients with compensated liver disease or patients with decompensated liver disease (pre- and post-transplant) in SOLAR-1 and SOLAR-2 trials, relapse was associated with the detection of one or more of the following NS5A RAVs: K24R, M28T, Q30R/H/K/E, L31V, H58D, and/or Y93H/C in 13/15 genotype 1a patients, and L31M, Y93H/N in 6/6 genotype 1b patients. No NS5A sequencing data was available from the remaining 3 patients who had low viral load (<1000IU/ml) at the last time point before discontinuation.

The NS5B nucleoside inhibitor resistance associated variants (NS5B NI RAVs) L159F and V321A were each detected in one patient in the Phase 3 trials. The single L159F and V321A variants demonstrated 1.2- and 1.2-fold change in EC_{50} to sofosbuvir in genotype 1a replicon, respectively. A NS5B substitution E237G was detected in 3 patients (1 genotype 1b and 2 genotype 1a) in the Phase 3 trials (ION-3, ION-1, and ION-2) and 3 patients (all genotype 1a) in the SOLAR-1 and SOLAR-2 trials at the time of relapse. The E237G substitution showed a 1.3-fold reduction in susceptibility to sofosbuvir in the genotype 1a replicon assay. The clinical significance of these substitutions is currently unknown.

The NS5B NI RAV S282T in NS5B was not detected in any failure isolate from the Phase 3 trials. However, the NS5B S282T substitution in combination with NS5A RAVs L31M, Y93H, and Q30L were detected in one patient at failure following 8 week treatment with HARVONI from a Phase 2 trial [LONESTAR]. This patient was subsequently retreated with HARVONI + RBV for 24 weeks and achieved SVR following retreatment.

Genotype 2, 3, 4, 5 and 6

Resistance analysis was performed for virologic failures in clinical trials with genotype 2, 3, 4, 5 and 6 CHC. Patients in these trials were treated with HARVONI or HARVONI + RBV for 12 weeks (see **CLINICAL TRIALS**).

Genotype 2: None of the genotype 2 patients experienced virologic failure in the LEPTON study.

Genotype 3: Of the 17 patients who experienced virologic failures in the ELECTRON-2 study, one patient developed the NS5A RAV Y93C (1.1%), one patient developed the NS5B NI RAV S282T and one patient developed the NS5B NI RAV L159F.

Genotype 4: Of the 3 patients who experienced virologic failure in Study 1119, one patient developed the NS5B NI RAV S282T along with the NS5A RAV Y93C. In the SOLAR-2 study, one patient with genotype 4d developed NS5B substitution E237G at the time of relapse. The clinical significance of this substitution is currently unknown.

Genotype 5: NS5A sequencing was successful in 1 of 2 virologic failure patients in Study 1119. This patient developed NS5B NI RAVs S282T (1.6%) and M289I (16%).

Genotype 6: Virologic failure occurred in one patient in the ELECTRON-2 study who discontinued treatment early at approximately Week 8 and subsequently relapsed in Study ELECTRON-2. This patient developed NS5B NI RAV S282T.

Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome

Adults

Genotype 1

Analyses were conducted to explore the association between pre-existing baseline NS5A resistance-associated variants (RAVs) and treatment outcome. In the pooled analysis of the Phase 3 trials, 256/1618 (16%) patients had baseline NS5A RAVs identified by population or deep sequencing irrespective of subtype. Of the 256 patients with NS5A RAVs, 235 (91.5%) achieved SVR12 following 8, 12, or 24 weeks of treatment with HARVONI (± RBV). The overall SVR12 rates in patients with baseline NS5A RAVs were 90.6% (174 of 192) for genotype 1a and 95.0% (57 of 60) for genotype 1b.

In genotype 1a treatment-naïve patients with NS5A RAVs (M28A, Q30H/R/E, L31M/V/I, H58D, Y93H/N/C), SVR12 rates of 89% (34/38) after 8 weeks and 96% (69/72) after 12 weeks of therapy were observed with HARVONI. All genotype 1b treatment-naïve patients with baseline NS5A RAVs (Y93H) achieved SVR12, regardless of treatment duration. Following HARVONI 12-week treatment, one of the 4 treatment-naïve patients who relapsed had L31M mutation at baseline while 11 other patients with L31M at baseline achieved SVR12.

In treatment-experienced patients in ION 2, a lower SVR rate of 69% (9 of 13) was observed among the small group of patients (n = 13) with NS5A RAVs conferring > 100-fold resistance to ledipasvir and who were treated with HARVONI for 12 weeks compared to 97% (93/96) in those without any baseline RAVs or RAVs conferring a fold-change of ≤100. All treatment-experienced patients with NS5A RAVs conferring ≤ 100-fold resistance had SVR12.

In HCV/HIV-1 co-infected patients in ION-4, 31 of the 34 patients (91.2%) with NS5A RAVs achieved SVR12, while 282 of 291 patients (96.9%) without NS5A RAVs achieved SVR12. For treatment-naïve patients, 33 of 34 patients (97.1%) with NS5A resistance-associated polymorphisms (RAPs) achieved SVR12, while 105 of 110 patients (95.5%) without NS5A RAPs achieved SVR12. For treatment-experienced patients, 45 of 49 patients (91.8%) with NS5A RAPs achieved SVR12, and 130 of 132 patients (98.5%) without NS5A RAPs achieved SVR12. In another study in treatment-experienced patients with compensated cirrhosis (SIRIUS, N=77), 8/8 (100%) patients with baseline N5SA RAVs conferring >100-fold reduced

susceptibility to ledipasvir achieved SVR following 12 weeks of treatment with HARVONI + RBV.

Among post-transplant patients with compensated liver disease (SOLAR-1 and SOLAR-2 studies), no relapse occurred in patients with baseline NS5A RAVs (N=23) following 12 weeks of treatment with HARVONI+RBV. Among patients with decompensated liver disease (pre- and post-transplant), 4/16 (25%) patients with NS5A RAVs conferring >100-fold resistance relapsed after 12 weeks treatment with HARVONI+RBV compared to 7/120 (6%) in those without any baseline NS5A RAVs or RAVs conferring a fold-change of ≤100.

The group of NS5A RAVs that conferred >100-fold shift and were observed in patients were the following substitutions in genotype 1a (M28A, Q30H/R/E, L31M/V/I, H58D, Y93H/N/C) or in genotype 1b (Y93H). Among treatment-experienced patients who relapsed, the following resistance associated variants were detected at baseline: Q30H/R, L31M, and/or Y93H/N.

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 trials by population or deep sequencing. SVR was achieved in all 24 patients (N=21 with L159F and N=3 with N142T) who had baseline NS5B NI RAVs.

Genotype 2, 3, 4, 5, and 6

Baseline NS5A RAVs did not have a clinically meaningful effect on treatment outcome in clinical studies of patients with genotype 2, 4, 5 or 6 CHC. For patients with genotype 3 CHC, the role of baseline NS5A RAVs varied depending on the patient population.

For patients with genotype 2, 4, 5 and 6 CHC, SVR was achieved in 14/14 (100%), 25/28 (89%), 7/8 (88%) and 17/18 (94%) patients who had baseline NS5A RAVs following 12 weeks treatment with HARVONI, respectively. The specific baseline NS5A RAVs observed in patients with virologic failure were L28M/V and L30R for genotype 4, L31M for genotype 5 and F28V for genotype 6.

Among treatment-naïve patients with genotype 3 CHC who were treated with HARVONI+RBV for 12 weeks, SVR was achieved in 4/4 (100%) patients with baseline NS5A RAVs. Among treatment-experienced patients with genotype 3 CHC, SVR was achieved in 4/6 (67%) and 37/44 (84%) patients with or without baseline NS5A RAVs, respectively. The specific baseline NS5A RAVs observed in patients with virologic failure were S24G, A30K, L31M and Y93H.

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient with genotype 2, 3, 4, 5 or 6 CHC in clinical trials by population or deep sequencing. For patients with genotype 2, 3 and 5 CHC, SVR was achieved in all 14 patients who had baseline NS5B NI RAVs (N=4 with M289I in genotype 2; N=1 with N142T in genotype 3; N=7 with N142T and N=2 with M289I in genotype 5).

Relapse occurred in 2/3 genotype 4 patients who had the baseline NS5B NI RAV V321I along with two baseline NS5A RAVs.

In patients with genotype 6 CHC, SVR was achieved in one patient each with the baseline NS5B NI RAVs M289L+S282G or M289L+V321A and 13/14 patients with M289L/I.

Pediatrics (12 to < 18 years of age)

The presence of NS5A and NS5B RAVs did not impact treatment outcome; all patients with baseline NS5A or NS5B NI RAVs achieved SVR following 12 weeks treatment with HARVONI.

Cross Resistance

Ledipasvir was fully active against the sofosbuvir resistance-associated substitution S282T in NS5B while all ledipasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors. *In vitro* studies demonstrated no cross resistance between sofosbuvir and ledipasvir when tested individually against HCV mutations resistant to other classes of HCV inhibitors. Both sofosbuvir and ledipasvir have been tested against an extensive panel of known resistance-associated variants (RAVs) to other classes of direct acting antivirals with different mechanisms of actions. These included NS3 RAVs affecting HCV protease inhibitors (ie, Q80K, R155K, A156T, and D168E/G/ V in genotype 1a; A156T and D168E/G/V in genotype 1b), and NS5B RAVs known to affect NNIs (ie. L419M/S, R422K, and M423I/T in genotypes 1a and 1b) and RBV (T390I and F415Y). No cross-resistance has been observed in these studies, and sofosbuvir and ledipasvir remain highly potent against RAVs affecting inhibitor classes other than their own. NS5A substitutions conferring resistance to ledipasvir may reduce the antiviral activity of other NS5A inhibitors. The efficacy of ledipasvir/sofosbuvir has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

Cytotoxicity

Sofosbuvir showed little or no cytotoxicity at the highest concentration tested (89 – 100 μM) in human cell lines derived from liver, prostate, lymphoid, or endothelial tissues or primary human cells isolated from the liver, circulating lymphoid cells, or bone marrow, except for Huh-7 cells where 50% cytotoxicity (CC_{50}) was observed at 66 μM.

Ledipasvir showed little or no cytotoxicity in multiple cell lines derived from liver, lymphoid or endothelial tissue. The CC_{50} values ranged from 2791 nM to > 50,000 nM in 1b-Rluc-2, Huh-luc, 1a-HRlucP, HepG2, MT4, and SL3 cell lines. Ledipasvir is therefore highly selective in cell-based replicon assays (Selectivity Index [SI] > 837,000-fold).

TOXICOLOGY

Repeat-Dose Toxicity

Ledipasvir
No target organs of toxicity were identified with ledipasvir. Ledipasvir was well tolerated in

studies for up to 4 weeks in the mouse, 6 months in the rat and 9 months in the dog. At the respective NOAELs, ledipasvir systemic exposure levels (sexes combined) were approximately 25-, 7-, and 7-fold greater in mice, rats, and dogs, respectively, than those in subjects treated with HARVONI. The only notable changes in the repeat dose toxicity studies were transient decreases in body weight gain and/or food consumption.

Sofosbuvir
Sofosbuvir or GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer, was evaluated in repeat-dose oral toxicity studies up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The primary target organs identified were the cardiovascular, hepatobiliary, gastrointestinal (GI) and hematopoietic (erythroid) systems. In 7-day toxicity studies with GS-9851, doses of 2000 mg/kg/day in the rat and 1500 mg/kg/day in the dog resulted in (but were not limited to) increased mucus secretions in the stomach, glycogen depletion, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, with associated histopathologic liver findings in dogs; and heart adverse effects in both rats (eg, multifocal cardiac myofiber degeneration) and dogs (eg, increased QT/QTc intervals). At the adverse dose, exposure levels (based on GS-331007 AUC) in the GS-9851 7-day toxicity studies were at least 28-fold higher than human exposure at 400 mg sofosbuvir. In a second 7-day toxicity study conducted with sofosbuvir alone in rats at doses up to 2000 mg/kg/day, no early mortalities or signs of cardiac toxicity were observed. GS-331007 exposure was 29-fold higher than human exposure at 400 mg sofosbuvir, a marginsimilar to that observed in the previous 7-day rat study with the stereomeric mixture (GS-9851). Findings in the liver and heart were not observed in long-term studies with GS-9851 or sofosbuvir. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), sofosbuvir effects included (but were not limited to) GI-related clinical signs (eg, soft feces and emesis) and a decrease (eg, approximately 10%) in mean red cell indices that were observed mainly in the high-dose group of dogs. One male dog was euthanized moribund with intestinal hemorrhage. The relationship to sofosbuvir was undetermined. In general, exposure levels in the chronic toxicity studies at the no observed adverse effect level were at least 9-fold (based on an AUC of GS-331007) higher than human exposure at 400 mg sofosbuvir.

Genotoxicity and Carcinogenicity

Ledipasvir
Ledipasvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rat micronucleus assays.

Ledipasvir was not carcinogenic in the 6-month rasH2 transgenic mouse and the 2-year rat carcinogenicity studies at exposures up to 26-times in mice and 8-times in rats higher than human exposure.

Sofosbuvir
Sofosbuvir, when administered as the diastereomeric mixture GS-9851, was not genotoxic in a bacterial mutagenicity assay, in an *in vitro* chromosome aberration test using human peripheral blood lymphocytes and in an *in vivo* mouse micronucleus assay.

Sofosbuvir was not carcinogenic in the 2-year mouse and rat carcinogenicity studies at doses resulting in GS-331007 exposures up to 17-times in mice and 9-times in rats, , higher than human exposure at 400 mg dose.

Reproductive and Development Toxicity

Ledipasvir
Ledipasvir had no adverse effects on mating and fertility. In female rats, the mean number of corpora lutea, and implantation sites were slightly reduced at maternal exposures 6-fold the exposure in humans at the recommended clinical dose. At the no observed effect level, AUC exposure to ledipasvir was approximately 7- and 3-fold, in males and females, respectively, the human exposure at the recommended clinical dose.

No teratogenic effects were observed in rat and rabbit developmental toxicity studies with ledipasvir.

In a rat pre- and postnatal study, at a maternally toxic dose, the developing rat offspring exhibited mean decreased body weight and body weight gain when exposed in utero (via maternal dosing) and during lactation (via maternal milk) at a maternal exposure approximately 4 times the exposure in humans at the recommended clinical dose. There were no effects on survival, physical and behavioral development and reproductive performance in the offspring at maternal exposures similar to the exposure in humans at the recommended clinical dose.

Sofosbuvir
Sofosbuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. No teratogenic effects were observed in rat and rabbit developmental toxicity studies with sofosbuvir. Sofosbuvir had no adverse effects on behavior, reproduction, or development of the offspring in the rat pre- and post-natal development study. At the highest dose tested where no adverse effects were observed, exposure to the predominant circulating metabolite GS-331007 was at least 5-fold the exposure in humans at the recommended clinical dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through lactation day 20 at daily GS-331007 exposures of approximately 7-fold higher than human exposures at the recommended clinical dose.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

HARVONI®

ledipasvir and sofosbuvir tablets

Read this carefully before you start taking **Harvoni**. Read it again every time you get a refill. This leaflet is a summary. It will not tell you everything about this drug. Talk to your doctor about your medical condition and treatment. Ask whether there is any new information about **Harvoni**.

Serious Warnings and Precautions

Hepatitis B activity (eg, inflamed liver) may increase when taking antiviral drugs like **Harvoni**, sometimes leading to liver failure and death. (See the "To help avoid side effects..." section, *Hepatitis B Reactivation*)

What is Harvoni used for?

- **Harvoni** treats chronic (lasting longer than 6 months) hepatitis C infection in adults and children 12 years of age and older.
- **Harvoni** may be used with ribavirin, but not always. Read the ribavirin patient medication information if your doctor says you should also take ribavirin.

How does Harvoni work?

Harvoni contains two medicines, ledipasvir and sofosbuvir, that have been combined together into one tablet (pill). This type of treatment course (regimen) is also known as a single tablet regimen. It provides a complete treatment for hepatitis C. For most patients, **Harvoni** does not need to be taken with either interferon or ribavirin.

- Ledipasvir and sofosbuvir block the virus from making more copies of itself in the body.
- **Harvoni** cures chronic hepatitis C in most patients. Cure means hepatitis C virus is cleared from your blood 3 months after finishing the medicine.
- Curing chronic hepatitis C can help lower the chance you will have liver problems or die from liver disease.

What are the ingredients in Harvoni?

Each tablet has the following medicines: ledipasvir, sofosbuvir.

Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

Each tablet is covered with the following ingredients that are not medicines: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Yellow #6/sunset yellow FCF aluminum lake.

Harvoni comes in the following dosage forms:
Harvoni comes in orange tablets. Each tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir.

Do not use Harvoni if:

- you are allergic to ledipasvir, sofosbuvir or any of the other ingredients in this product. (Read also "What are the ingredients in **Harvoni**?" above.)
- your doctor says you should use ribavirin with Harvoni and you are pregnant or may become pregnant (or if your partner is pregnant or may become pregnant). Ribavirin may cause birth defects or the death of your unborn baby.

To help avoid side effects and make sure you take your medicine properly, talk to your doctor before you take Harvoni. Talk about any health problems you may have, including if you:

- have liver problems other than hepatitis C infection.
- have had a liver transplant.
- have HIV.
- have severe kidney disease or you are on dialysis.
- are pregnant or plan to become pregnant (see "***Pregnancy and Birth Control***" below).
- are breastfeeding or plan to breastfeed. Do NOT breastfeed while taking **Harvoni**.
- are taking anything listed in the section "**The following may interact with Harvoni**".
- if you were born with one of the rare problems of galactose intolerance (severe lactase deficiency or glucose/galactose malabsorption). **Harvoni** contains lactose.

Hepatitis B Reactivation

Taking antiviral drugs such as **Harvoni** may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Contact your doctor if:

- you have never been tested for hepatitis B.
- you know you have a current hepatitis B infection.
- you have had a previous hepatitis B infection.

Your healthcare provider may do blood tests:

- before hepatitis C treatment.
- to see the hepatitis B levels in your blood.
- and may order hepatitis B treatment.

Ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy and Birth Control

If you are pregnant or plan to become pregnant, ask your doctor for advice before taking this medicine. It is NOT known if **Harvoni** will harm your unborn baby.

Harvoni may be used with ribavirin. Ribavirin may cause birth defects and death of the unborn baby. Extreme care must be taken to avoid becoming pregnant.

- Females must have a negative pregnancy test before starting **Harvoni** and ribavirin, every month while on these medicines, and for 6 months after stopping them.
- You or your partner should not become pregnant while taking **Harvoni** with ribavirin and for 6 months after you have stopped taking them.
- You and your partner must use 2 kinds of birth control while taking **Harvoni** and ribavirin and for 6 months after you have stopped taking them.
- Talk to your doctor about the kind of birth control you can use.
- If you or your partner becomes pregnant while taking **Harvoni** with ribavirin or within 6 months after you stop taking them, tell your doctor right away.

Another warning you should know about:

Because **Harvoni** already contains sofosbuvir, do not take **Harvoni** with any other medicines containing sofosbuvir (eg, Sovaldi®).

Tell your doctor about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Harvoni:

- antacids (like Tums®, Rolaids® or Alka-Seltzer®) or medicines that have an ingredient to protect the stomach, used for heartburn and indigestion.
- amiodarone (Cordarone®), a drug used to treat certain irregular heartbeats (see "**What are possible side effects from using Harvoni?**").
- carbamazepine (Tegretol®), a drug used to treat seizures, nerve pain and bipolar disorder.
- digoxin (Lanoxin®, Toloxin®), a drug used to treat congestive heart failure.
- tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, STRIBILD®, TRUVADA®, VIREAD®), to treat HIV.
- medicines for indigestion, heartburn or ulcers. Examples are nizatidine (Axid®), famotidine (Pepcid AC®, Peptic Guard®, Ulcidine®), cimetidine (Tagamet®), ranitidine (Zantac®), esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Losec®), rabeprazole (Aciphex®) and pantoprazole (Pantoloc®).
- oxcarbazepine (Trileptal®), a drug used to control seizures.
- phenobarbital, a drug used to treat anxiety and to control seizures.
- phenytoin (Dilantin®), a drug used to control seizures.

- rifabutin (Mycobutin®), a drug used to treat tuberculosis.
- rifampin (Rifadin®, Rifater®, Rofact®), a drug used to treat tuberculosis.
- rosuvastatin (Crestor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- simeprevir (Galexos®), a drug used to treat hepatitis C.
- St. John's wort (*Hypericum perforatum*), an herbal product used for anxiety or depression.
- tipranavir (Aptivus®) or tipranavir/ritonavir (Aptivus® and Norvir®), drugs used to treat HIV.

How to take Harvoni:

- Take this medicine with or without food.
- Your doctor will determine how long you need to take this medicine. It can be for 8, 12 or 24 weeks.
- If you are taking an antacid, you may need to take **Harvoni** at a different time than the antacid. Talk to your doctor.
- Do NOT stop taking **Harvoni** without first talking with your doctor.

Usual dose: Adults and children 12 years of age and older

- Take one tablet once each day.

Overdose:

If you think you have taken too much **Harvoni**, contact your doctor or pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

It is important to take **Harvoni** each day.

- **If you miss a dose** of **Harvoni** and you notice within 18 hours, take a tablet as soon as you can. Then take the next dose at your usual time.
- **If you miss a dose** of **Harvoni** and you notice after 18 hours, wait and take the next dose at your usual time. Do NOT take a double dose (two doses close together).

What to do if you vomit (throw up):

- If you vomit **less than 5 hours** after taking **Harvoni**, take another tablet.
- If you vomit **more than 5 hours** after taking **Harvoni**, wait. Do NOT take another tablet until you are scheduled to take the next tablet.

What are possible side effects from using Harvoni?

If your side effect is not listed here, contact your doctor.
The most common side effects of **Harvoni** are: feeling tired and headache.

When **Harvoni** is used with amiodarone (a heart drug), side effects may be:

- slow heartbeat leading to a need for a pacemaker or death. (see "**Serious side effects and what to do about them**" table below for symptoms)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Slow heartbeat (bradycardia) when taken with amiodarone (Cordarone®) with symptoms such as:** • near fainting or fainting • dizziness or lightheadedness • not feeling well • feeling weak or very tired • shortness of breath • chest pains • confusion or memory problems		✓ ✓ ✓ ✓ ✓ ✓ ✓	
Serious Allergic Reactions: skin rashes with or without blisters, swelling of the face, lips, tongue or throat, trouble breathing		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your doctor.

Reporting side effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

NOTE: Contact your doctor if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store **Harvoni** below 30°C (86°F).
- Keep **Harvoni** in its original container.
- Do NOT use **Harvoni** if the seal over the bottle opening is broken or missing.
- Keep this medication where children cannot reach it or see it.

If you want more information about Harvoni:

- Talk to your doctor or pharmacist.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website www.gilead.ca, or by calling 1-800-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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Gilead Sciences, Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

e170097-GS-008

THE ATTACHED IS EXHIBIT "F" TO THE

AFFIDAVIT OF HEATHER RUMBLE PETERSON

SWORN BEFORE ME THIS 13TH DAY OF

OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrHOLKIRA® PAK

ombitasvir/paritaprevir/ritonavir
film-coated tablets (12.5/75/50 mg)

and

dasabuvir (as dasabuvir sodium monohydrate)
film-coated tablets (250 mg)

Antiviral Agent

Date of Preparation:
December 22, 2014

Date of Previous Revision:
February 13, 2017

Date of Revision:
March 27, 2017

AbbVie Corporation
8401 Trans-Canada Highway
St-Laurent, Qc H4S 1Z1

Submission Control No: 201441

Table of Contents

PrHOLKIRA PAK

ombitasvir/paritaprevir/ritonavir and dasabuvir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	ombitasvir/paritaprevir /ritonavir film-coated tablets: 12.5/75/50 mg	None
	dasabuvir film-coated tablets: 250 mg (as dasabuvir sodium monohydrate)	Lactose monohydrate
		*For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) is indicated for the treatment of adults with genotype 1 chronic hepatitis C (CHC) infection, including those with compensated cirrhosis:

- with ribavirin in non-cirrhotic and cirrhotic patients with genotype 1a infection;
- without ribavirin in non-cirrhotic and cirrhotic patients with genotype 1b infection

Geriatrics (> 65 years of age):

In Phase 3 clinical trials, 8.5% (174/2053) of patients were age 65 or over. No overall differences in safety or effectiveness were observed between these patients and younger patients (see **WARNINGS AND PRECAUTIONS**).

HCV Patients Co-Infected with HIV-1:

Efficacy and safety of HOLKIRA PAK has been established in patients with hepatitis C virus (HCV) genotype 1 co-infected with HIV-1 (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

Post-Liver Transplant Recipients:

Efficacy and safety of HOLKIRA PAK with ribavirin has been established in liver transplant recipients with normal hepatic function and Metavir fibrosis score of ≤ 2, regardless of the HCV genotype 1 subtype (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

Pediatrics (< 18 years of age):

Safety and effectiveness of HOLKIRA PAK in children less than 18 years of age have not been established (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

- Patients who are hypersensitive to the medicinal ingredients of HOLKIRA PAK (ombitasvir, paritaprevir, ritonavir and dasabuvir) or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING.**
- Patients with known hypersensitivity (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir.
- If HOLKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen (see the ribavirin Product Monograph for a list of contraindications for ribavirin).
- The use of ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant, may be pregnant, or plan to become pregnant because of the risks for birth defects and fetal death associated with ribavirin (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).
- HOLKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) due to risk of potential toxicity.
- The following categories of drugs are contraindicated with HOLKIRA PAK:
    - Drugs for which elevated plasma concentrations are associated with serious adverse events and that are sensitive cytochrome P450 (CYP) 3A substrates;
    - Drugs that are strong CYP2C8 inhibitors, which may increase dasabuvir plasma concentrations;
    - Drugs that are moderate or strong inducers of CYP3A, which may result in substantial lowering of plasma concentrations of paritaprevir, ombitasvir and dasabuvir.

- Drugs that are strong inducers of CYP2C8, which may result in substantial lowering of plasma concentrations of dasabuvir.

Table 1. Drugs that Are Contraindicated with HOLKIRA PAK

Drug Class	Drug Name
Alpha1-adrenoreceptor antagonist	alfuzosin HCl
Antiarrhythmic	dronedarone
Antibiotic	fusidic acid (oral formulation)*
Anticonvulsants	carbamazepine, phenytoin, phenobarbital
Anti-gout	colchicine in patients with renal and/or hepatic impairment
Antihistamine	astemizole, terfenadine*
Antihyperlipidemic	gemfibrozil
Antimycobacterial	rifampin
Antipsychotic	lurasidone
Antiviral	efavirenz-containing regimens, including Atripla, etravirine, nevirapine
Benzodiazepines	oral midazolam, triazolam
Endothelin receptor agonist	bosentan
Ergot derivatives	ergotamine, dihydroergotamine, ergonovine*, methylergonovine*
GI Motility Agent	cisapride*
Herbal Product	St. John's Wort (*Hypericum perforatum*)
Hormonal Product	ethinyl estradiol-containing medications such as combined oral contraceptives
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin
Long-acting beta-adrenoceptor agonist	salmeterol
Neuroleptics	pimozide
PDE5 enzyme inhibitor	sildenafil only when used for the treatment of pulmonary arterial hypertension (PAH)
Others	modafinil

* Drugs not sold in Canada.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Potential for Hepatitis B virus (HBV) reactivation:** Screen all patients for evidence of current or prior HBV infection before initiating HOLKIRA PAK therapy. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct-acting HCV antivirals (DAAs) in patients co-infected with HBV. (See **WARNINGS AND PRECAUTIONS, Potential for Hepatitis B Virus Reactivation**)

General

If HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) is administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen. (see the ribavirin Product Monograph).

HOLKIRA PAK contains ritonavir and should not be co-administered with additional ritonavir or ritonavir-containing regimens.

Co-administration of HOLKIRA PAK with other direct-acting antivirals (DAAs) against HCV has not been studied and therefore cannot be recommended.

As a fixed dose combination formulation, no dosage adjustments for HOLKIRA PAK are possible.

Retreatment of patients previously treated with HOLKIRA PAK or other DAAs is not recommended since the efficacy in these patients has not been established.

Transaminase Elevations with Concomitant Drugs

Clinically significant transaminase elevations were observed when HOLKIRA PAK was co-administered with efavirenz- or ethinyl estradiol-containing regimens and therefore these drugs are contraindicated with HOLKIRA PAK (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Table 5**). When HOLKIRA PAK is co-administered with other drugs known to cause elevations of transaminases, caution should be exercised and monitoring of transaminase levels should be considered. If transaminase elevations occur, consideration should be given to whether the other drug may be discontinued. Discontinuation of HOLKIRA PAK should be considered if there are clinical signs of liver inflammation that are accompanied by persistent elevations in ALT, direct bilirubin or international normalized ratio (INR) (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, ALT Elevations**).

Use with Tacrolimus

Co-administration of HOLKIRA PAK with systemic tacrolimus increases the concentrations of tacrolimus via CYP3A inhibition (see **DRUG INTERACTIONS, Table 9**). Serious and/or life threatening adverse events have been observed with co-administration of HOLKIRA PAK with systemic tacrolimus. Avoid concomitant use of tacrolimus with HOLKIRA PAK unless the benefits outweigh the risks.

If tacrolimus and HOLKIRA PAK are used concomitantly, tacrolimus should not be administered on the day HOLKIRA PAK is initiated. Beginning the day after HOLKIRA PAK is initiated reinitiate tacrolimus at a reduced dose based on tacrolimus whole blood concentrations. The recommended tacrolimus dose is 0.5 mg every 7 days (see **DRUG INTERACTIONS, Table 6**).

Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with HOLKIRA PAK and the dose and/or dosing frequency should be adjusted as needed. Patients should be monitored frequently for any changes in renal function or tacrolimus-associated adverse events. Refer to the tacrolimus Product Monograph for additional dosing and monitoring instructions.

Use with Fluticasone (and other glucocorticoids metabolized by CYP3A)

Use caution when administering HOLKIRA PAK with fluticasone or other glucocorticoids that are metabolized by CYP3A4 (see **DRUG INTERACTIONS, Table 7**). Concomitant use of inhaled glucocorticoids metabolized by CYP3A can increase systemic exposures of the glucocorticoids, and cases of Cushing's syndrome and subsequent adrenal suppression have been reported with ritonavir-containing regimens. Concomitant use of HOLKIRA PAK and glucocorticoids, particularly long-term use, should only be initiated if the potential benefit of treatment outweighs the risk of systemic corticosteroid effects.

Use with Quetiapine

The use of HOLKIRA PAK with quetiapine, a CYP3A4 substrate, is not recommended due to an expected increase in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose and monitor for quetiapine-associated adverse reactions (see **DRUG INTERACTIONS, Table 6** and the quetiapine Product Monograph for the recommendations on adverse reaction monitoring).

Use with Rilpivirine

Concomitant use of HOLKIRA PAK with rilpivirine, a CYP3A4 substrate, significantly increased rilpivirine exposure by 243%. Co-administration of HOLKIRA PAK with rilpivirine is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine (see **DRUG INTERACTIONS, Table 6**).

Use with HMG-CoA Reductase Inhibitors

Simvastatin and lovastatin, CYP3A4 substrates, are contraindicated with HOLKIRA PAK (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Table 5**). Concomitant use of atorvastatin or rosuvastatin with HOLKIRA PAK should be avoided; for patients receiving fluvastatin, use the lowest dose or switch to low-dose pravastatin (see **DRUG INTERACTIONS, Table 7**).

Cardiovascular

QTc Prolongation

HOLKIRA PAK was associated with concentration-dependent QTc prolongation. At therapeutic plasma concentrations, the maximum mean difference from placebo in the QTc interval was reported to be < 5 ms, with a 95% CI upper limit of < 10 ms (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Effects on Electrocardiogram**).

Caution should be exercised when drugs that prolong QTc are co-administered with HOLKIRA PAK (see **DRUG INTERACTIONS**).

Hepatic/Biliary/Pancreatic

Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis

Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported from postmarketing sources in patients treated with HOLKIRA PAK with and without ribavirin. Most patients with these severe outcomes had evidence of advanced or decompensated cirrhosis prior to initiating therapy. Reported cases typically occurred within one to four weeks of initiating therapy and were characterized by the acute onset of rising direct serum bilirubin levels without ALT elevations in association with clinical signs and symptoms of hepatic decompensation. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

HOLKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) (see **CONTRAINDICATIONS; DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Hepatic Impairment; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

For patients with cirrhosis:

- Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal hemorrhage).

- Hepatic laboratory testing including direct bilirubin levels should be performed at baseline, during the first 4 weeks of starting treatment and as clinically indicated thereafter.

- Discontinue treatment in patients who develop evidence of hepatic decompensation.

ALT Elevations

During clinical trials with HOLKIRA PAK with or without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all patients (see **ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings, Laboratory Abnormalities**). **These ALT elevations were significantly more frequent in female patients who were using ethinyl estradiol-containing medications such as combined oral contraceptives or contraceptive vaginal rings (see CONTRAINDICATIONS).** ALT elevations typically occurred during the first 4 weeks of treatment and declined within approximately two weeks of onset with continued dosing of HOLKIRA PAK with or without ribavirin.

Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with HOLKIRA PAK (see CONTRAINDICATIONS). Alternative contraceptive agents or methods of contraception (e.g, progestin only contraception or non-hormonal methods) are recommended during HOLKIRA PAK therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with HOLKIRA PAK.

Patients using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy, had a rate of ALT elevation similar to those not receiving any estrogens (1%). However, due to the limited number of patients taking these other estrogens (n=87), caution is warranted for co-administration with HOLKIRA PAK.

Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice and discolored feces. If elevated liver chemistries are identified, careful follow-up is recommended. HOLKIRA PAK should be discontinued if there are clinical signs of liver inflammation that are accompanied by persistent elevations in ALT, direct bilirubin or international normalized ratio (INR).

Potential for Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV–coinfected patients who were undergoing, or completed treatment with DAA. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patient with serologic evidence of resolved HBV infection (i.e. HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage

potential for HBV reactivation (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Renal

No dose adjustment of HOLKIRA PAK is required in patients with mild, moderate, or severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

HOLKIRA PAK has not been studied in patients on dialysis. For patients that require ribavirin, refer to the ribavirin Product Monograph for information regarding use in patients with renal impairment .

Sexual Function/Reproduction

Fertility

There are no studies on the effect of HOLKIRA PAK on human fertility.

No effects on fertility were observed in animal studies with the components of HOLKIRA PAK (see **NON-CLINICAL TOXICOLOGY, Fertility**).

Use with Ribavirin in Females and Males of Reproductive Potential

Ribavirin may cause birth defects and/or death of the exposed fetus (see **CONTRAINDICATIONS**). Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients when HOLKIRA PAK is administered in combination with ribavirin as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin.

HOLKIRA PAK in combination with ribavirin should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use at least two effective forms of contraception during treatment and for at least 6 months after treatment has concluded. See additional information on specific hormonal contraceptives in **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, ALT Elevations;** and **DRUG INTERACTIONS, Table 7.** Routine monthly pregnancy tests must be performed during this time (see the ribavirin Product Monograph).

Special Populations

Pregnant Women

HOLKIRA PAK with Ribavirin

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, ribavirin is contraindicated in women who are pregnant and in men whose female partners are pregnant (see **CONTRAINDICATIONS** and the ribavirin Product Monograph).

HOLKIRA PAK

There are no studies with HOLKIRA PAK in pregnant women.

No effects on embryo-fetal development have been noted in studies in animals with paritaprevir/ritonavir, ombitasvir and its major inactive human metabolites (M29, M36) or dasabuvir. For paritaprevir/ritonavir, the highest doses tested produced exposures equal to 98-fold (mouse) or 8-fold (rat) the exposures in humans at the recommended clinical dose. For ombitasvir, the highest dose tested produced exposures equal to 28-fold (mouse) or 4-fold (rabbit) the exposure in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26 times higher in mice than in humans at the recommended clinical dose. For dasabuvir, the highest dose tested produced exposures equal to 24-fold (rat) or 6-fold (rabbit) the exposure in humans at the recommended clinical dose.

Ombitasvir, paritaprevir and dasabuvir were minimally transferred through the placenta of pregnant rats.

Nursing Women

It is not known whether paritaprevir/ritonavir, ombitasvir or dasabuvir and their metabolites are excreted in human breast milk. Paritaprevir and its hydrolysis product M13, unchanged ombitasvir and dasabuvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups. A risk to the newborn cannot be excluded; therefore nursing must be discontinued prior to initiation of treatment with HOLKIRA PAK. Physicians prescribing ribavirin should also refer the patient to the Product Monograph for ribavirin.

Pediatrics (< 18 years of age)

Safety and effectiveness of HOLKIRA PAK in children less than 18 years of age have not been established.

Geriatrics (> 65 years of age)

No dose adjustment of HOLKIRA PAK is needed in geriatric patients. In Phase 3 clinical trials, 8.5% (174/2053) of patients were age 65 or over. No overall differences in safety or

effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

HCV-HBV Co-infection

The safety and efficacy of HOLKIRA PAK have not been established in HCV patients co-infected with HBV. HBV reactivation has been reported during treatment and post-treatment with DAAs in patients co-infected with HBV who were not undergoing treatment for HBV infection (see **WARNINGS AND PRECAUTIONS, Potential for Hepatitis B Virus Reactivation**).

HCV-HIV Co-infection

The ritonavir component of HOLKIRA PAK is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with HOLKIRA PAK should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

HOLKIRA PAK is contraindicated with efavirenz-containing regimens (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Table 5**).

Other HCV Genotypes

The safety and efficacy of HOLKIRA PAK has not been established in patients with HCV genotypes other than genotype 1.

Use in Patients Who Have Failed Previous Therapy with Direct-Acting Antivirals against HCV

HOLKIRA PAK efficacy has not been studied in patients who have previously failed therapy with other direct-acting antiviral (DAA) agents.

Monitoring and Laboratory Tests

For patients with cirrhosis, hepatic laboratory testing including direct bilirubin levels should be performed at baseline, during the first 4 weeks of starting treatment and as clinically indicated thereafter. Discontinue treatment in patients who develop evidence of hepatic decompensation.

Refer to **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** for additional information.

Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV coinfected. Co-infected patients should be monitored for clinical and laboratory signs (e.g. HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS, Potential for Hepatitis B Virus Reactivation**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety summary is based on pooled data from phase 2 and 3 clinical trials in more than 2,600 patients who received HOLKIRA PAK with or without ribavirin.

In patients receiving HOLKIRA PAK with ribavirin, the most commonly reported treatment emergent adverse events considered related to study drug by site investigator (greater than 10% of patients) were fatigue, headache, nausea, pruritus and insomnia. The proportion of patients who permanently discontinued treatment due to related adverse events was 0.8% (17/2,044). 0.5% (11/2,044) of patients interrupted treatment due to related adverse events. 3.5% (72/2,044) of patients had ribavirin dose reductions due to related adverse events.

The safety profile of HOLKIRA PAK and ribavirin in patients with cirrhosis was similar to that of patients without cirrhosis.

In patients receiving HOLKIRA PAK without ribavirin, the most commonly reported treatment emergent adverse events considered related to study drug by site investigator (greater than 10% of patients) were fatigue and headache. No patients permanently discontinued treatment due to a related adverse event and no patients had a treatment interruption due to a related adverse event.

In patients with genotype 1b infection and compensated cirrhosis receiving HOLKIRA PAK without ribavirin, the most commonly reported treatment emergent adverse event considered related to study drug by site investigator (greater than 10% of patients) was fatigue. One patient (2%) had a serious adverse event. One patient (2%) interrupted treatment due to a related adverse event and no patients permanently discontinued treatment due to adverse events. Post-baseline Grade 2 increases in total bilirubin occurred in 12/60 (20%) patients.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Table 2 lists adverse drug reactions (Grades 2 to 4) observed in ≥ 3% of patients in the Phase 3 trials.

The majority of adverse events in the Phase 3 clinical trials were of grade 1 severity. The safety profile of HOLKIRA PAK with ribavirin was consistent with the known safety profile of ribavirin.

Table 2. Side-by-Side Tabulation of Adverse Reactions (Grade 2 – 4) in ≥ 3% of Patients in Phase 3*

	SAPPHIRE I and II (patients without cirrhosis)		PEARL II, III and IV (patients without cirrhosis)		TURQUOISE II (patients with cirrhosis)	TURQUOISE III (patients with cirrhosis)
Adverse Reaction	HOLKIRA PAK + RBV 12 Weeks N = 770 n (%)	Placebo 12 Weeks N = 255 n (%)	HOLKIRA PAK + RBV 12 Weeks N = 401 n (%)	HOLKIRA PAK 12 Weeks N = 509 n (%)	HOLKIRA PAK + RBV 12 or 24 Weeks N = 380 n (%)	HOLKIRA PAK 12 Weeks N = 60 n (%)
Fatigue	29 (3.8)	4 (1.6)	26 (6.5)	22 (4.3)	15 (3.9)	4 (6.7)
Nausea	26 (3.4)	2 (0.8)	2 (0.5)	2 (0.4)	8 (2.1)	0
Asthenia	22 (2.9)	3 (1.2)	6 (1.5)	1 (0.2)	12 (3.2)	0
Headache	35 (4.5)	6 (2.3)	10 (2.5)	12 (2.4)	12 (3.2)	3 (5.0)

* Frequencies of adverse events are based on treatment-emergent adverse events considered at least possibly related to study drug by site investigators.

HCV-HIV-1 Co-infected Patients

The overall safety profile in HCV genotype 1/HIV-1 co-infected patients was similar to that observed in HCV genotype 1 mono-infected patients. Transient elevations in total bilirubin > 3 × ULN (mostly indirect) occurred in 17/63 (27.0%) patients; 15 of these patients were receiving atazanavir. None of the patients with hyperbilirubinemia had concomitant elevations of aminotransferases.

Liver Transplant Recipients

The type of adverse events experienced by HCV genotype 1 infected liver transplant recipients who were treated with HOLKIRA PAK and ribavirin (in addition to their immunosuppressant medications) was similar to those experienced by patients treated with HOLKIRA PAK with ribavirin in Phase 3 clinical trials; however some events were increased in frequency. Adverse events occurring in > 20% of post-liver transplant patients included fatigue 50.0% (17/34), headache 44.1% (15/34), cough 32.4% (11/32), diarrhea 26.5% (9/34), insomnia 26.5% (9/34), asthenia 23.5% (8/34), nausea 23.5% (8/34), anemia 20.6% (7/34), muscle spasms 20.6% (7/34), and rash 20.6% (7/34). Ten patients (29.4%) had at least one post-baseline hemoglobin value of less than 10 g/dL. Ten of 34 patients (29.4%) had dose modified due to decrease in hemoglobin and 2.9% (1/34) had an interruption of ribavirin. Ribavirin dose modification did not impact SVR rates. Five patients required erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No patient received a blood transfusion.

Less Common Clinical Trial Adverse Drug Events (< 3%)

Treatment emergent adverse events (Grades 2 to 4) considered at least possibly related to study drug by site investigators which occurred in less than 3% of patients in Phase 3 trials are listed below by system organ class (**Table 3**).

Table 3. Adverse Events (Grade 2 – 4) in < 3% of Patients in Phase 3

Body System	Adverse Events
Blood and lymphatic system disorders:	anaemia, leukopenia, neutropenia
Cardiac disorders:	extrasystoles, palpitations, sinus tachycardia, tachycardia, ventricular extrasystoles
Ear and labyrinth disorders:	tinnitus
Endocrine disorders:	goitre, hypothyroidism, thyroiditis, adrenal insufficiency
Eye disorders:	blepharitis, ulcerative keratitis, visual impairment
Gastrointestinal disorders:	abdominal discomfort, abdominal pain, abdominal pain upper, anorectal discomfort, constipation, dental caries, diarrhoea, dry mouth, dyspepsia, dysphagia, frequent bowel movements, gastrointestinal disorder, gastrooesophageal reflux disease, haemorrhoids, hyperchlorhydria, lip ulceration, pancreatitis, retching, vomiting
General disorders and administration site conditions:	chest discomfort, chills, energy increased, exercise tolerance decreased, hunger, inflammation, influenza like illness, irritability, malaise, oedema peripheral, pain, pre-existing condition improved, product taste abnormal, pyrexia, swelling
Hepatobiliary disorders:	hyperbilirubinaemia, jaundice
Immune system disorders:	seasonal allergy
Infections and infestations:	abscess, bronchitis, cellulitis, ear infection, gastroenteritis, gingival infection, herpes simplex, lower respiratory tract infection, nasopharyngitis, oral herpes, sinusitis, skin infection, upper respiratory tract infection, tooth abscess
Investigations:	alanine aminotransferase increased, blood bilirubin increased, blood bilirubin unconjugated increased, irritability, malaise, electrocardiogram abnormal, haemoglobin decreased, neutrophil count increased, reticulocyte count increased, transaminases increased, weight decreased, white blood cell count decreased
Metabolism and nutrition disorders:	decreased appetite, diabetes mellitus, gout, hyperphosphataemia, hypertriglyceridaemia, hypophosphataemia, increased appetite, lactic acidosis
Musculoskeletal and connective tissue disorders:	arthralgia, arthritis, axillary mass, back pain, bone pain, bursitis, muscle spasms, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, neck pain, pain in extremity, sensation of heaviness, tendonitis
Nervous system disorders:	ataxia, cerebrovascular accident, disturbance in attention, dizziness, dysgeusia, hyperaesthesia, intention tremor, lethargy, memory impairment, migraine, neuralgia, paraesthesia, presyncope, restless legs syndrome, somnolence, syncope, tension headache, tremor

Body System	Adverse Events
Psychiatric disorders:	abnormal dreams, affect lability, agitation, anger, anxiety, anxiety disorder, depressed mood, depression, emotional disorder, euphoric mood, insomnia, libido decreased, mental status changes, mood altered, mood swings, nervousness, nightmare, sleep disorder, suicidal ideation, tearfulness, terminal insomnia
Reproductive system and breast disorders:	amenorrhoea, menorrhagia, metrorrhagia
Respiratory thoracic and mediastinal disorders:	acute respiratory failure, chronic obstructive pulmonary disease, cough, dyspnoea, dyspnoea exertional, hypoxia, respiratory depression, sleep apnoea syndrome
Skin and subcutaneous tissue disorders:	alopecia, blister, cold sweat, dandruff, dry skin, erythema, night sweats, photodermatosis, photosensitivity reaction, pruritus, pruritus generalised, rash, rash erythematous, rash generalised, rash papular, rash pruritic, skin odour abnormal, skin reaction
Vascular disorders:	flushing, hot flush, hypertension, hypotension

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

Changes in selected laboratory parameters are described in **Table 4**. A side-by-side tabulation is provided to simplify presentation; direct comparisons should not be made across trials that differ in design.

Table 4. **Selected Treatment Emergent Laboratory Abnormalities of at Least Moderate Intensity (Grades 2-4)**

Laboratory Parameters	SAPPHIRE I and II (patients without cirrhosis)		PEARL II, III and IV (patients without cirrhosis)		TURQUOISE II (patients with cirrhosis)	TURQUOISE III (patients with cirrhosis)
	HOLKIRA PAK + RBV 12 Weeks N = 770 n (%)	Placebo 12 Weeks N = 255 n (%)	HOLKIRA PAK + RBV 12 Weeks N = 401 n (%)	HOLKIRA PAK 12 Weeks N = 509 n (%)	HOLKIRA PAK + RBV 12 or 24 Weeks N = 380 n (%)	HOLKIRA PAK 12 Weeks N = 60 n (%)
ALT						
> 5-20 × ULN* (Grade 3)	6/765 (0.8%)	10/254 (3.9%)	3/401 (0.7%)	1/509 (0.2%)	4/380 (1.1%)	1/60 (1.7%)
> 20 × ULN (Grade 4)	3/765 (0.4%)	0	0	0	2/380 (0.5%)	0
Hemoglobin						
< 10-8 g/dL (Grade 2)	41/765 (5.4%)	0	23/401 (5.7%)	0	30/380 (7.9%)	1/60 (1.7%)
< 8-6.5 g/dL (Grade 3)	1/765 (0.1%)	0	2/401 (0.5%)	0	3/380 (0.8%)	0
< 6.5 g/dL (Grade 4)	0	0	0	0	1/380 (0.3%)	0
Total Bilirubin						
> 3-10 × ULN (Grade 3)	19/765 (2.5%)	0	23/401 (5.7%)	2/509 (0.4%)	37/380 (9.7%)	0
> 10 × ULN (Grade 4)	1/765 (0.1%)	0	0	0	0	0

* ULN: Upper Limit of Normal according to testing laboratory.

Serum ALT Elevations

During clinical trials with HOLKIRA PAK with and without ribavirin, less than 1% of patients who were not on ethinyl estradiol-containing medications experienced transient serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment (see **CONTRAINDICATIONS**). These elevations were asymptomatic, generally occurred during the first 4 weeks of treatment and resolved with ongoing therapy. Increases in ALT were not associated with simultaneous increases in bilirubin levels. Cirrhosis was not a risk factor for elevated ALT. No specific monitoring of liver chemistries is required for the majority of patients (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, ALT Elevations**).

Serum Bilirubin Elevations

Transient elevations in bilirubin (predominantly indirect) were observed in patients receiving HOLKIRA PAK with ribavirin, related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced hemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with aminotransferase elevations. The frequency of indirect bilirubin elevations was lower among patients who did not receive ribavirin.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post approval use of HOLKIRA PAK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity reactions (including tongue and lip swelling).

Hepatobiliary Disorders: Hepatic decompensation, hepatic failure (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

DRUG INTERACTIONS

Drug-Drug Interactions

Potential for HOLKIRA PAK to Affect Other Drugs

Ritonavir is a strong inhibitor of CYP3A. Co-administration of HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of these drugs. Drugs that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious events are contraindicated (see **CONTRAINDICATIONS**).

Paritaprevir is an inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3, and paritaprevir and ritonavir are inhibitors of OATP2B1. Paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Co-administration of HOLKIRA PAK with drugs that are substrates of OATP1B1, OATP1B3, OATP2B1 or BCRP may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring.

While paritaprevir, ritonavir and dasabuvir are *in vitro* inhibitors of P-gp, only slight increase was observed in the exposure of the P-gp substrate, digoxin, when administered with HOLKIRA PAK. Monitoring for plasma concentrations of drugs that are sensitive for changed intestinal P-gp activity is recommended.

Ombitasvir, paritaprevir and dasabuvir are inhibitors of UGT1A1. Co-administration of HOLKIRA PAK with drugs that are primarily metabolized by UGT1A1 is expected to result in increased plasma concentrations of such drugs; consider clinical monitoring for narrow therapeutic index drugs (i.e. levothyroxine). See also **Table 5** for specific advice on raltegravir and buprenorphine, which have been evaluated in drug interaction studies.

Co-administration of HOLKIRA PAK can decrease exposures of drugs that are primarily metabolized by CYP2C19 (e.g., omeprazole). Clinical monitoring and/or dose increases might be needed for CYP2C19 substrates when administered with HOLKIRA PAK.

HOLKIRA PAK did not affect the exposures of the CYP2C9 substrate, warfarin, or CYP2D6/CYP1A2 substrate, duloxetine. Dose adjustment is not required for CYP2C9 or CYP2D6 or CYP1A2 substrates when administered with HOLKIRA PAK.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir do not inhibit organic anion transporter (OAT1) *in vivo* as shown by the lack of interaction with tenofovir (OAT1 substrate). *In vitro* studies show that ombitasvir, paritaprevir, ritonavir and dasabuvir are not inhibitors of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations. Therefore, HOLKIRA PAK is not expected to affect drugs which are primarily excreted by the renal route via these transporters.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir are not expected to inhibit organic cation transporter 1 (OCT1) at clinically relevant concentrations.

Caution should be exercised when drugs that prolong QTc are co-administered with HOLKIRA PAK.

Potential for Other Drugs to Affect HOLKIRA PAK

Paritaprevir and ritonavir are primarily metabolized by CYP3A, and dasabuvir is primarily metabolized by CYP2C8.

Strong inhibitors of CYP3A may significantly increase paritaprevir and ritonavir exposures when co-administered with HOLKIRA PAK. Drugs that potently inhibit CYP2C8 may significantly increase dasabuvir plasma concentrations; the co-administration of HOLKIRA PAK with a weak CYP2C8 inhibitor trimethoprim did not meaningfully affect dasabuvir exposure.

Drugs that induce CYP3A are expected to decrease dasabuvir, paritaprevir, ombitasvir and ritonavir plasma concentrations significantly and reduce their therapeutic effect. Drugs that induce CYP2C8 are expected to decrease dasabuvir plasma concentrations significantly and reduce its therapeutic effect. Drugs that are strong CYP2C8 inhibitors, CYP3A inducers or CYP2C8 inducers are contraindicated with HOLKIRA PAK (see **CONTRAINDICATIONS**).

Paritaprevir, dasabuvir, ritonavir and ombitasvir are substrates of P-gp. Paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may significantly increase exposures of the various components of HOLKIRA PAK.

Paritaprevir is a substrate of CYP3A and transport proteins. Caution is advised if co-administering HOLKIRA PAK with products that are both moderate inhibitors of CYP3A4 and inhibitors of multiple transporters (P-gp, BCRP and/or OATP1B1/ OATP1B3) as it can result in clinically relevant increases in paritaprevir exposures.

Drugs that Are Contraindicated with HOLKIRA PAK

The drugs that are contraindicated with HOLKIRA PAK are listed in **Table 5**.

Table 5. Drugs that Are Contraindicated with HOLKIRA PAK

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ALPHA1-ADRENORECEPTOR ANTAGONISTS		
alfuzosin HCL	CYP3A inhibition by ritonavir	Potential for increased alfuzosin concentrations which can result in hypotension.
ANTIARRHYTHMICS		
dronedarone	CYP3A inhibition by ritonavir	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias
ANTIBIOTICS		
fusidic acid (oral formulation)*	CYP3A4 inhibition by ritonavir	Potential for increased fusidic acid concentrations with risk of adverse events such as hepatotoxicity.
ANTICONVULSANTS		
carbamazepine, phenytoin, phenobarbital	CYP3A4 induction by carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.
ANTI-GOUT		
colchicine	CYP3A4 inhibition by ritonavir	Contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions. For recommendations concerning patients with normal renal and hepatic function see **Table 7.**
ANTIHISTAMINES		
astemizole, terfenadine*	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias.
ANTIHYPERLIPIDEMICS		
gemfibrozil	CYP2C8 inhibition by gemfibrozil	Increased risk of QT prolongation due to 10-fold increase in dasabuvir AUC

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ANTIMYCOBACTERIALS		
rifampin	CYP3A4/CYP2C8 induction by rifampin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.
ANTIPSYCHOTICS		
lurasidone	CYP3A inhibition by ritonavir	Potential for serious and/or life-threatening reactions.
BENZODIAZEPINES		
oral midazolam, triazolam	CYP3A4 inhibition by ritonavir	Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
ENDOTHELIN RECEPTOR ANTAGONISTS		
bosentan	CYP3A4 induction by bosentan	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.
ERGOT DERIVATIVES		
ergotamine, dihydroergotamine, ergonovine*, methylergonovine*	CYP3A4 inhibition by ritonavir	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
GI MOTILITY AGENTS		
cisapride*	CYP3A4 inhibition by ritonavir	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
HERBAL PRODUCTS		
St. John's Wort (*Hypericum perforatum*)	CYP3A4 induction by St. John's Wort	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.
HIV-ANTIVIRAL AGENTS		
efavirenz-containing regimens, such as Atripla,		Co-administration of efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla) with paritaprevir, ritonavir and dasabuvir was poorly tolerated and resulted in liver enzyme elevations and early study termination.
nevirapine, etravirine	CYP3A4 induction by nevirapine or etravirine	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.
HORMONAL PRODUCTS		
ethinyl estradiol-containing drugs (combined oral contraceptives, contraceptive vaginal rings, contraceptive patch)	possibly due to UGT inhibition by ombitasvir and paritaprevir	Potential for ALT elevations.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
HMG CoA REDUCTASE INHIBITORS		
lovastatin, simvastatin	CYP3A4 and OATP1B inhibition by ritonavir and paritaprevir, respectively	Potential for serious reactions such as myopathy including rhabdomyolysis.
LONG-ACTING BETA-ADRENOCEPTOR AGONISTS		
salmeterol	CYP3A4 inhibition by ritonavir	Potential for QT prolongation, palpitations and sinus tachycardia.
NEUROLEPTICS		
pimozide	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias.
PDE5 ENZYME INHIBITORS		
sildenafil only at the doses used daily for the treatment of pulmonary arterial hypertension	CYP3A4 inhibition by ritonavir	Potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
OTHER		
modafinil	CYP3A4 induction by modafinil	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.

* Drugs not sold in Canada

Drugs that Should not be Co-administered with HOLKIRA PAK

The drugs that should not be co-administered with HOLKIRA PAK are listed in **Table 6.**

Table 6. Drugs that Should not be Co-administered with HOLKIRA PAK

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ANTIARRHYTHMICS		
amiodarone, disopyramide, flecainide, lidocaine (systemic), propafenone, quinidine	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias. Physicians considering combined therapy of HOLKIRA PAK with amiodarone should refer to the amiodarone Product Monograph, carefully weigh the potential benefits and risks, and monitor patients for amiodarone-associated adverse reactions.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ANTIPSYCHOTICS		
quetiapine	CYP3A4 inhibition by ritonavir	Potential for an increase in quetiapine exposure. If the co-administration is necessary, reduce the quetiapine dose and closely monitor patients for quetiapine-associated adverse reactions (see the quetiapine Product Monograph).
HIV-ANTIVIRAL AGENTS		
darunavir/ritonavir	unknown	Potential for reduced therapeutic activity of HOLKIRA PAK. For administration of HOLKIRA PAK with darunavir without additional ritonavir, refer to **Table 7.**
rilpivirine	CYP3A4 inhibition by ritonavir	Potential for QT interval prolongation due to increased rilpivirine exposure.
ritonavir and ritonavir-containing regimens, including atazanavir/ritonavir, lopinavir/ritonavir	CYP3A4 inhibition by ritonavir	Potential for increased paritaprevir exposure. For administration of HOLKIRA PAK with atazanavir without ritonavir, refer to **Table 7.**
IMMUNOSUPPRESSANTS		
sirolimus	CYP3A4 inhibition by ritonavir	Increase in sirolimus exposure (see **Table 9**) for which no adequate dose adjustment recommendations can be provided.
everolimus	CYP3A4 inhibition by ritonavir	Should not be co-administered due to a significant increase in everolimus exposures that cannot be properly dose-adjusted with available dose strengths.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
tacrolimus	CYP3A4 inhibition by ritonavir	Co-administration of HOLKIRA PAK with systemic tacrolimus increases the concentrations of tacrolimus via CYP3A inhibition (see Table 9). Serious and/or life threatening adverse events have been observed with co-administration of HOLKIRA PAK with systemic tacrolimus. Avoid concomitant use of tacrolimus with HOLKIRA PAK unless the benefits outweigh the risks. If tacrolimus and HOLKIRA PAK are used concomitantly, tacrolimus should not be administered on the day HOLKIRA PAK is initiated. Beginning the day after HOLKIRA PAK is initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. The recommended tacrolimus dosing is 0.5 mg every 7 days (see **WARNINGS AND PRECAUTIONS**). Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with HOLKIRA PAK and the dose and/or dosing frequency should be adjusted as needed. Upon completion of HOLKIRA PAK treatment, the appropriate dose and dosing frequency of tacrolimus should be guided by assessment of tacrolimus blood concentrations.
OPIOID ANALGESICS		
alfentanil, fentanyl	CYP3A4 inhibition by ritonavir	Potential for increased opioid exposure.

Established and Other Potential Drug Interactions

Table 7 lists clinically relevant drug interactions where patient monitoring and/or dose adjustment are recommended. The pharmacokinetic data relevant to these drug interactions are shown in **Table 8** and **Table 9**.

Table 7. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of HOLKIRA PAK or Concomitant Drug	Clinical comments
ANGIOTENSIN RECEPTOR BLOCKERS		
candesartan, losartan and valsartan	↑ candesartan, ↑ losartan ↑ valsartan	Decrease the dose of the angiotensin receptor blockers and monitor patients.

Concomitant Drug Class: Drug Name	Effect on Concentration of HOLKIRA PAK or Concomitant Drug	Clinical comments
ANTIARRHYTHMICS		
digoxin	↑ digoxin	While no dose adjustment is necessary for digoxin, appropriate monitoring of serum digoxin levels is recommended.
ANTICOAGULANTS		
warfarin	↓ warfarin	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalized ratio (INR) is recommended.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole ↑ paritaprevir	Caution is warranted, and patients should be monitored for adverse reactions to ketoconazole and HOLKIRA PAK. The maximum daily dose of ketoconazole should not exceed 200 mg.
itraconazole and posaconazole (not studied, theoretical)	↑ itraconazole ↑ posaconazole ↑ paritaprevir	Drug interactions similar to ketoconazole are expected; monitor patients for adverse reactions and reduce the dose of the co-administered drug as appropriate.
voriconazole (not studied, theoretical)	↓ voriconazole ↑ paritaprevir	Co-administration of HOLKIRA PAK with voriconazole is expected to decrease voriconazole exposure and to increase paritaprevir exposure. Co-administration is not recommended unless the assessment of the benefit-to-risk ratio justifies the use of voriconazole.
ANTI-GOUT		
colchicine		Contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions (see **CONTRAINDICATIONS**). A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with HOLKIRA PAK is required (see also the colchicine Product Monograph).
CALCIUM CHANNEL BLOCKERS		
amlodipine	↑ amlodipine	Caution is warranted and a 50% reduction in the dose of amlodipine should be considered.

Concomitant Drug Class: Drug Name	Effect on Concentration of HOLKIRA PAK or Concomitant Drug	Clinical comments
diltiazem, nifedipine and verapamil	↑ diltiazem ↑ nifedipine ↑ verapamil	Decrease the dose of the calcium channel blocker. Clinical monitoring of patients is recommended.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone		Concomitant use of HOLKIRA PAK with inhaled or nasal fluticasone may decrease serum cortisol concentrations. Cases of Cushing's syndrome and adrenal suppression have been reported with ritonavir-containing regimens. Alternative corticosteroids should be considered, particularly for long term use.
DIURETICS		
furosemide	↑ furosemide	Caution and monitoring for furosemide clinical effects are recommended; decrease the dose of furosemide by up to 50% if clinically indicated.
HIV-ANTIVIRAL AGENTS		
atazanavir	atazanavir administered in the morning ↔ atazanavir ↑ paritaprevir	Atazanavir without ritonavir should be co-administered at the same time as HOLKIRA PAK. The ritonavir in HOLKIRA PAK will provide atazanavir boosting. Atazanavir plus ritonavir is not recommended with HOLKIRA PAK.
darunavir	↓ darunavir (C_{trough})	Darunavir without ritonavir should be co-administered at the same time as HOLKIRA PAK. The ritonavir in HOLKIRA PAK will provide darunavir boosting. Because of decreased darunavir trough concentrations, patients should be monitored for HIV-1viral breakthrough.
raltegravir	↑ raltegravir	No dose adjustment is necessary for raltegravir.
HMG CoA REDUCTASE INHIBITORS		
fluvastatin	↑ fluvastatin	The lowest dose of fluvastatin should be used. Monitor patients for fluvastatin side effects such as myopathy/rhabdomyolysis.
rosuvastatin	↑ rosuvastatin	Co-administration of rosuvastatin with HOLKIRA PAK should be avoided. If used together, caution should be exercised and patients should be monitored for rosuvastatin side effects such as myopathy/rhabdomyolysis. Rosuvastatin dose should not exceed 5 mg per day.
pravastatin	↑ pravastatin	Pravastatin dose should not exceed 40 mg per day. Patients should be monitored for pravastatin side effects such as myopathy/rhabdomyolysis.

Concomitant Drug Class: Drug Name	Effect on Concentration of HOLKIRA PAK or Concomitant Drug	Clinical comments
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine	When starting co-administration with HOLKIRA PAK, give one fifth of the total daily dose of cyclosporine once daily with HOLKIRA PAK. Monitor cyclosporine levels and adjust dose and/or dosing frequency as needed.
MUSCLE RELAXANTS		
carisoprodol	↓ carisoprodol ↔ mepobramate (metabolite of carisoprodol)	Monitor patients for decreased efficacy of carisoprodol; increase the carisoprodol dose if clinically indicated.
cyclobenzaprine	↓ cyclobenzaprine ↓ norcyclobenzaprine (metabolite of cyclobenzaprine)	Monitor patients for decreased efficacy of cyclobenzaprine; increase the cyclobenzaprine dose if clinically indicated.
NARCOTIC ANALGESICS		
buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine (metabolite of buprenorphine)	No dose adjustment of buprenorphine/naloxone is required.
hydrocodone (when co-administered as a fixed-dose combination of 300 mg acetaminophen/5 mg hydrocodone)	↑ hydrocodone	Hydrocodone dose should be reduced by 50%. Monitor patients for respiratory depression and sedation at frequent intervals.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Monitor patients for decreased efficacy of omeprazole; increase the omeprazole dose if clinically indicated.
SEDATIVES/HYPNOTICS		
alprazolam	↑ alprazolam	Caution is warranted and clinical monitoring of patients for alprazolam-associated side effects is recommended. A decrease in alprazolam dose can be considered based on clinical response.
diazepam	↓ diazepam ↓ nordiazepam (metabolite of diazepam)	Monitor patients for decreased efficacy of diazepam; increase the diazepam dose if clinically indicated.

The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC)

Drugs with No Observed Interactions with HOLKIRA PAK

Drug interaction studies in patients reveal no clinically significant interaction between HOLKIRA PAK and the following commonly co-prescribed medications. No dose adjustments are required when co-administering these drugs with HOLKIRA PAK: abacavir, acetaminophen, dolutegravir, duloxetine, emtricitabine, escitalopram, lamivudine, metformin, methadone, naloxone, norethindrone, sofosbuvir, sulfamethoxazole, tenofovir disoproxil fumarate, trimethoprim, zolpidem.

Pharmacokinetic Parameters for Clinically Relevant Drug Interactions

Change in pharmacokinetic parameters for drug interaction for drug interactions resulting in contraindications, dose modification or clinical monitoring is presented in **Table 8** and **Table 9**. **Table 8** provides the magnitude of interaction on the concomitant medication. For information regarding clinical recommendations, see **Table 7**.

Table 8. Drug Interactions: Change in Pharmacokinetic Parameters of the Individual Components of HOLKIRA PAK in the Presence of co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
ANTIARRHYTHMICS						
digoxin	0.5 single dose	12	dasabuvir	0.99 (0.92-1.07)	0.97 (0.91-1.02)	0.99 (0.92-1.07)
			ombitasvir	1.03 (0.97-1.10)	1.00 (0.98-1.03)	0.99 (0.96-1.02)
			paritaprevir	0.92 (0.80-1.06)	0.94 (0.81-1.08)	0.92 (0.82-1.02)
			ritonavir	1.01 (0.94, 1.08)	0.98 (0.94, 1.03)	0.96 (0.89, 1.04)
ANTICOAGULANTS						
warfarin	5 single dose	12	dasabuvir	0.97 (0.89-1.06)	0.98 (0.91-1.06)	1.03 (0.94-1.13)
			ombitasvir	0.94 (0.89-1.00)	0.96 (0.93-1.00)	0.98 (0.95-1.02)
			paritaprevir	0.98 (0.82-1.18)	1.07 (0.89-1.27)	0.96 (0.85-1.09)
			ritonavir	0.94 (0.89, 1.00)	0.97 (0.94. 1.00)	1.10 (1.03, 1.17)
ANTICONVULSANTS						
carbamazepine	200 once daily followed by 200 twice daily	12	dasabuvir	0.45 (0.41, 0.50)	0.30 (0.28, 0.33)	NA
			ombitasvir	0.69 (0.61, 0.78)	0.69 (0.64, 0.74)	NA
			paritaprevir	0.34 (0.25, 0.48)	0.30 (0.23, 0.38)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ritonavir	0.17 (0.12, 0.24)	0.13 (0.09, 0.17)	NA
ANTIFUNGALS						
ketoconazole	400 once daily	12	dasabuvir	1.16 (1.03, 1.32)	1.42 (1.26, 1.59)	NA
			ombitasvir	0.98 (0.90, 1.06)	1.17 (1.11, 1.24)	NA
			paritaprevir	1.37 (1.11, 1.69)	1.98 (1.63, 2.42)	NA
			ritonavir	1.27 (1.04, 1.56)	1.57 (1.36, 1.81)	NA
ANTIHYPERLIPIDEMIC AGENT						
gemfibrozil[a]	600 twice daily	11	dasabuvir	2.01 (1.71, 2.38)	11.25 (9.05, 13.99)	NA
			ombitasvir	NA	NA	NA
			paritaprevir	1.21 (0.94, 1.57)	1.38 (1.18, 1.61)	NA
			ritonavir	0.84 (0.69, 1.03)	0.90 (0.78, 1.04)	NA
CALCIUM CHANNEL BLOCKERS						
amlodipine	5 single dose	14	dasabuvir	1.05 (0.97, 1.14)	1.01 (0.96, 1.06)	0.95 (0.89, 1.01)
			ombitasvir	1.00 (0.95, 1.06)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
			paritaprevir	0.77 (0.64, 0.94)	0.78 (0.68, 0.88)	0.88 (0.80, 0.95)
			ritonavir	0.96 (0.87, 1.06)	0.93 (0.89, 0.98)	0.95 (0.89, 1.01)
CONTRACEPTIVES						
ethinylestradiol/ norgestimate	0.035/0.25 once daily	7[b]	dasabuvir	0.51 (0.22-1.18)	0.48 (0.23-1.02)	0.53 (0.30- 0.95)
			ombitasvir	1.05 (0.81-1.35)	0.97 (0.81-1.15)	1.00 (0.88- 1.12)
			paritaprevir	0.70 (0.40-1.21)	0.66 (0.42-1.04)	0.87 (0.67-1.14)
			ritonavir	0.80 (0.53, 1.21)	0.71 (0.54, 0.94)	0.79 (0.68, 0.93)
nor-ethindrone (progestin only pill)	0.35 once daily	12	dasabuvir	1.01 (0.90-1.14)	0.96 (0.85-1.09)	0.95 (0.80-1.13)
			ombitasvir	1.00 (0.93-1.08)	0.99 (0.94-1.04)	0.97 (0.90-1.03)
			paritaprevir	1.24 (0.95-1.62)	1.23 (0.96-1.57)	1.43 (1.13-1.80)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ritonavir	1.01 (0.89, 1.13)	1.08 (0.95, 1.23)	1.27 (1.06, 1.51)
DIURETICS						
furosemide	20 single dose	12	dasabuvir	1.12 (0.96, 1.31)	1.09 (0.96, 1.23)	1.06 (0.98, 1.14)
			ombitasvir	1.14 (1.03, 1.26)	1.07 (1.01, 1.12)	1.12 (1.08, 1.16)
			paritaprevir	0.93 (0.63, 1.36)	0.92 (0.70, 1.21)	1.26 (1.16, 1.38)
			ritonavir	1.10 (0.96, 1.27)	1.04 (0.92, 1.18)	1.07 (0.99, 1.17)
HIV-ANTIVIRAL AGENTS						
atazanavir/ ritonavir[c]	Atazanavir 300 and ritonavir 100 once daily in the evening	11	dasabuvir	0.81 (0.73, 0.91)	0.81 (0.71, 0.92)	0.80 (0.65, 0.98)
			ombitasvir	0.83 (0.72, 0.96)	0.90 (0.78, 1.02)	1.00 (0.89, 1.13)
			paritaprevir	2.19 (1.61, 2.98)	3.16 (2.40, 4.17)	11.95 (8.94, 15.98)
			ritonavir	1.60 (1.38, 1.86)	3.18 (2.74, 3.69)	24.65 (18.64, 32.60)
darunavir[d]	800 once daily	9	dasabuvir	1.10 (0.88, 1.37)	0.94 (0.78, 1.14)	0.90 (0.76, 1.06)
			ombitasvir	0.86 (0.77, 0.95)	0.86 (0.79, 0.94)	0.87 (0.82, 0.92)
			paritaprevir	1.54 (1.14, 2.09)	1.29 (1.04, 1.61)	1.30 (1.09, 1.54)
			ritonavir	0.84 (0.72, 0.98)	0.85 (0.78, 0.93)	1.07 (0.93, 1.23)
darunavir/ ritonavir[e]	Darunavir 600 twice daily and ritonavir 100 once daily in the evening	7	dasabuvir	0.84 (0.67, 1.05)	0.73 (0.62, 0.86)	0.54 (0.49, 0.61)
			ombitasvir	0.76 (0.65, 0.88)	0.73 (0.66, 0.80)	0.73 (0.64, 0.83)
			paritaprevir	0.70 (0.43, 1.12)	0.59 (0.44, 0.79)	0.83 (0.69, 1.01)
			ritonavir	1.61 (1.30, 2.00)	1.28 (1.12, 1.45)	0.88 (0.79, 0.99)
darunavir/ ritonavir[f]	Darunavir 800 and ritonavir 100 once daily in the evening	12	dasabuvir	0.75 (0.64, 0.88)	0.72 (0.64, 0.82)	0.65 (0.58, 0.72)
			ombitasvir	0.87 (0.82, 0.93)	0.87 (0.81, 0.93)	0.87 (0.80, 0.95)
			paritaprevir	0.70 (0.50, 0.99)	0.81 (0.60, 1.09)	1.59 (1.23, 2.05)
			ritonavir	1.19 (1.06, 1.33)	1.70 (1.54, 1.88)	14.15 (11.66, 17.18)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
lopinavir/ ritonavir	400/100 twice daily	6	dasabuvir	0.99 (0.75, 1.31)	0.93 (0.75, 1.15)	0.68 (0.57, 0.80)
			ombitasvir	1.14 (1.01, 1.28)	1.17 (1.07, 1.28)	1.24 (1.14, 1.34)
			paritaprevir	2.04 (1.30, 3.20)	2.17 (1.63, 2.89)	2.36 (1.00, 5.55)
			ritonavir	1.55 (1.16, 2.09)	2.05 (1.49, 2.81)	5.25 (3.33, 8.28)
lopinavir/ ritonavir[g]	800/200 once daily	12	dasabuvir	0.56 (0.47, 0.66)	0.54 (0.46, 0.65)	0.47 (0.39, 0.58)
			ombitasvir	0.87 (0.83, 0.92)	0.97 (0.94, 1.02)	1.11 (1.06, 1.16)
			paritaprevir	0.99 (0.79, 1.25)	1.87 (1.40, 2.52)	8.23 (5.18, 13.07)
			ritonavir	1.57 (1.34, 1.83)	2.62 (2.32, 2.97)	19.46 (15.93, 23.77)
rilpivirine	25 once daily (morning)[g]	10	dasabuvir	1.18 (1.02, 1.37)	1.17 (0.99, 1.38)	1.10 (0.89, 1.37)
			ombitasvir	1.11 (1.02, 1.20)	1.09 (1.04, 1.14)	1.05 (1.01, 1.08)
			paritaprevir	1.30 (0.94, 1.81)	1.23 (0.93, 1.64)	0.95 (0.84, 1.07)
			ritonavir	1.10 (0.98, 1.24)	1.08 (0.93, 1.27)	0.97 (0.91, 1.04)
HMG CoA REDUCTASE INHIBITORS						
pravastatin	10 once daily	12	dasabuvir	1.00 (0.87, 1.14)	0.96 (0.85, 1.09)	1.03 (0.91, 1.15)
			ombitasvir	0.95 (0.89-1.02)	0.89 (0.83-0.95)	0.94 (0.89-0.99)
			paritaprevir	0.96 (0.69, 1.32)	1.13 (0.92, 1.38)	1.39 (1.21, 1.59)
			ritonavir	0.89 (0.73, 1.09)	0.95 (0.86, 1.05)	1.08 (0.98, 1.19)
rosuvastatin	5 once daily	11	dasabuvir	1.07 (0.92, 1.24)	1.08 (0.92, 1.26)	1.15 (1.05, 1.25)
			ombitasvir	0.92 (0.82, 1.04)	0.89 (0.83, 0.95)	0.88 (0.83, 0.94)
			paritaprevir	1.59 (1.13, 2.23)	1.52 (1.23, 1.90)	1.43 (1.22, 1.68)
			ritonavir	0.98 (0.84, 1.15)	1.02 (0.93, 1.12)	1.00 (0.90, 1.12)
IMMUNOSUPPRESSANTS						
cyclosporine	30 single dose[i]	10	dasabuvir	0.66 (0.58, 0.75)	0.70 (0.65, 0.76)	0.76 (0.71, 0.82)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ombitasvir	0.99 (0.92, 1.07)	1.08 (1.05, 1.11)	1.15 (1.08, 1.23)
			paritaprevir	1.44 (1.16, 1.78)	1.72 (1.49, 1.99)	1.85 (1.58, 2.18)
			ritonavir	0.90 (0.78, 1.04)	1.11 (1.04, 1.19)	1.49 (1.28, 1.74)
tacrolimus	2 single dose	12	dasabuvir	0.85 (0.73, 0.98)	0.90 (0.80, 1.02)	1.01 (0.91, 1.11)
			ombitasvir	0.93 (0.88, 0.99)	0.94 (0.89, 0.98)	0.94 (0.91, 0.96)
			paritaprevir	0.57 (0.42, 0.78)	0.66 (0.54, 0.81)	0.73 (0.66, 0.80)
			ritonavir	0.76 (0.63, 0.91)	0.87 (0.79, 0.97)	1.03 (0.89, 1.19)
MUSCLE RELAXANTS						
carisoprodol	250 single dose	14	dasabuvir	0.96 (0.91, 1.01)	1.02 (0.97, 1.07)	1.00 (0.92, 1.10)
			ombitasvir	0.98 (0.92, 1.04)	0.95 (0.92, 0.97)	0.96 (0.92, 0.99)
			paritaprevir	0.88 (0.75, 1.03)	0.96 (0.85, 1.08)	1.14 (1.02, 1.27)
			ritonavir	0.94 (0.87, 1.02)	0.94 (0.88, 0.99)	0.95 (0.89, 1.03)
cyclobenzaprine	5 single dose	14	dasabuvir	0.98 (0.90, 1.07)	1.01 (0.96, 1.06)	1.13 (1.07, 1.18)
			ombitasvir	0.98 (0.92, 1.04)	1.00 (0.97, 1.03)	1.01 (0.98, 1.04)
			paritaprevir	1.14 (0.99, 1.32)	1.13 (1.00, 1.28)	1.13 (1.01, 1.25)
			ritonavir	0.93 (0.87, 0.99)	1.00 (0.95, 1.06)	1.13 (1.05, 1.21)
NARCOTIC ANALGESICS						
hydrocodone/ acetaminophen	5/300 single dose	15	dasabuvir	1.13 (1.01, 1.26)	1.12 (1.05, 1.19)	1.16 (1.08, 1.25)
			ombitasvir	1.01 (0.93, 1.10)	0.97 (0.93, 1.02)	0.93 (0.90, 0.97)
			paritaprevir	1.01 (0.80, 1.27)	1.03 (0.89, 1.18)	1.10 (0.97, 1.26)
			ritonavir	1.01 (0.90, 1.13)	1.03 (0.96, 1.09)	1.01 (0.93, 1.10)
PROTON PUMP INHIBITORS						
omeprazole	40 once daily	11	dasabuvir	1.13 (1.03, 1.25)	1.08 (0.98, 1.20)	1.05 (0.93, 1.19)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ombitasvir	1.02 (0.95, 1.09)	1.05 (0.98, 1.12)	1.04 (0.98, 1.11)
			paritaprevir	1.19 (1.04, 1.36)	1.18 (1.03, 1.37)	0.92 (0.76, 1.12)
			ritonavir	1.04 (0.96, 1.12)	1.02 (0.97, 1.08)	0.97 (0.89, 1.05)
SEDATIVES/HYPNOTICS						
alprazolam	0.5 single dose	12	dasabuvir	0.93 (0.83, 1.04)	0.98 (0.87, 1.11)	1.00 (0.87, 1.15)
			ombitasvir	0.98 (0.93, 1.04)	1.00 (0.96, 1.04)	0.98 (0.93, 1.04)
			paritaprevir	0.91 (0.64, 1.31)	0.96 (0.73, 1.27)	1.12 (1.02, 1.23)
			ritonavir	0.92 (0.84, 1.02)	0.96 (0.89, 1.03)	1.01 (0.94, 1.09)

a. Study was conducted with paritaprevir, ritonavir and dasabuvir.

b. N = 3 for dasabuvir

c. Atazanavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of the components of HOLKIRA PAK.

d. Darunavir administered with the components of HOLKIRA PAK in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.

e. Darunavir administered with the components of HOLKIRA PAK in the morning and with 100 mg ritonavir in the evening was compared to darunavir administered with 100 mg ritonavir in the morning and evening.

f. Darunavir plus 100 mg ritonavir administered in the evening, 12 hours after the morning dose of the components of HOLKIRA PAK compared to darunavir administered with 100 mg ritonavir in the evening.

g. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of the components of HOLKIRA PAK.

h. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.

i. 30 mg cyclosporine was administered with the components of HOLKIRA PAK in the test arm and 100 mg cyclosporine was administered in the reference arm without the components of HOLKIRA PAK.

NA: not available/not applicable; DAA: Direct-acting antiviral agent; CI: Confidence interval

Doses of dasabuvir were 250 mg or 400 mg (both doses showed similar exposures). Doses of ombitasvir, paritaprevir, and ritonavir were 25 mg, 150 mg and 100 mg.

Dasabuvir was dosed twice daily and ombitasvir, paritaprevir and ritonavir were dosed once daily in all the above studies except studies with gemfibrozil, ketoconazole and carbamazepine that used single doses.

Table 9 summarizes the effects of HOLKIRA PAK on the pharmacokinetics of co-administered drugs which showed clinically relevant changes. For information regarding clinical recommendations, see **Table 7**.

Table 9. Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Components of HOLKIRA PAK

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without Components of HOLKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{trough}
alprazolam	0.5	1 day	12	1.09 (1.03, 1.15)	1.34 (1.15, 1.55)	NA
amlodipine	5	1 day	14	1.26 (1.11, 1.44)	2.57 (2.31, 2.86)	NA
Buprenorphine	Buprenorphine : 4 to 24 once daily and Naloxone 1 to 6 once daily	14 days	10	2.18 (1.78, 2.68)[c]	2.07 (1.78, 2.40)[c]	3.12 (2.29, 4.27)[c]
naloxone				1.18 (0.81, 1.73)	1.28 (0.92, 1.79)[c]	NA
carisoprodol	250	1 day	14	0.54 (0.47, 0.63)	0.62 (0.55, 0.70)	NA
carisoprodol's metabolite, mepobramate				1.17 (1.10, 1.25)	1.09 (1.03, 1.16)	NA
cyclobenzaprine	5	1 day	14	0.68 (0.61, 0.75)	0.60 (0.53, 0.68)	NA
cyclobenzaprine's metabolite norcyclobenzaprine				1.03 (0.87, 1.23)	0.74 (0.64, 0.85)	NA
cyclosporine	30[h]	1 day	10	1.01 (0.85, 1.20)	5.69 (4.67, 6.93)	15.80 (13.81, 18.09)[a, b]
everolimus	0.75	1 day	12	4.74 (4.29, 5.25)	27.12 (24.5, 30.1)	16.10 (14.5, 17.9)[g]
darunavir	800 once daily	14 days	8	0.92 (0.87, 0.98)[d]	0.76 (0.71, 0.82)[d]	0.52 (0.47, 0.58)[d]
darunavir/ritonavir[e]	Darunavir 800 and ritonavir 100 once daily in the evening	14 days	10	0.79 (0.70, 0.90)[d]	1.34 (1.25, 1.43)[d]	0.54 (0.48, 0.62)[d]
Darunavir/ ritonavir[d]	Darunavir 600 twice daily and ritonavir 100 once daily in the evening	14 days	7	0.87 (0.79, 0.96)[b]	0.80 (0.74, 0.86)[b]	0.57 (0.48, 0.67)[b]

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without Components of HOLKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{trough}
diazepam	2	1 day	13	1.18 (1.07, 1.30)	0.78 (0.73, 0.82)	NA
diazepam's metabolite nordiazepam				1.10 (1.03, 1.19)	0.56 (0.45, 0.70)	NA
digoxin	0.5	1 day	12	1.15 (1.04,1.27)	1.16 (1.09,1.23)	1.01 (0.97,1.05)
ethinylestradiol	0.035/0.25 once daily	12 days	9	1.16 (0.90,1.50)	1.06 (0.96,1.17)	1.12 (0.94,1.33)
norgestimate				2.26 (1.91,2.67)	2.54 (2.09,3.09)	2.93 (2.39,3.57)
norgestimate metabolites: norgestrel and norelgestromin				2.01 (1.77,2.29)	2.60 (2.30,2.95)	3.11 (2.51,3.85)
furosemide	20	1 day	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	NA
hydrocodone	5	1 day	15	1.27 (1.14, 1.40)	1.90 (1.72, 2.10)	NA
ketoconazole	400	1 day	12	1.15 (1.09, 1.21)	2.17 (2.05, 2.29)	NA
lopinavir/ritonavir	400/100 twice daily	14 days	6	0.87 (0.76, 0.99)[d]	0.94 (0.81, 1.10)[d]	1.15 (0.93, 1.42)[d]
lopinavir/ritonavir	800/200 once daily	14 days	12	0.86 (0.80, 0.93)[d]	0.94 (0.87, 1.01)[d]	3.18 (2.49, 4.06)[d]
omeprazole	40	1 day	11	0.62 (0.48, 0.80)	0.62 (0.51, 0.75)	NA
pravastatin	10	14 days	12	1.37 (1.11, 1.69)	1.82 (1.60, 2.08)	NA
rilpivirine	25 (morning)	14 days	20	2.55 (2.08, 3.12)	3.25 (2.80, 3.77)	3.62 (3.12, 4.21)
	25 (evening)	14 days	20	2.16 (1.79, 2.61)	2.50 (2.05, 3.06)	2.87 (2.28, 3.62)
	25 (night: 4 hrs after dinner)	14 days	20	3.00 (2.50, 3.59)	3.43 (3.03, 3.89)	3.73 (3.16, 4.40)
rosuvastatin	5	14 days	11	7.13 (5.11, 9.96)	2.59 (2.09, 3.21)	0.59 (0.51, 0.69)

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without Components of HOLKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{trough}
sirolimus	0.5[e]	1 day	11	6.40 (5.34, 7.68)[c]	37.99 (31.5, 45.8)[c]	19.55 (16.7, 22.9)[c, b]
tacrolimus	2	1 day	12	3.99 (3.21, 4.97)	57.13 (45.5, 71.7)	16.56 (12.97, 21.16)[a, b]
R-warfarin	5	1 day	12	1.05 (0.95,1.17)	0.88 (0.81,0.95)	0.94 (0.84,1.05)
S-warfarin				0.96 (0.85,1.08)	0.88 (0.81,0.96)	0.95 (0.88,1.02)

NA: Not available

a. Dose normalized parameters reported.

a. C_{24}: concentration at 24 hours following single dose of cyclosporine, digoxin, sirolimus or tacrolimus.

b. Dose normalized parameters reported.

c. Atazanavir or darunavir or lopinavir parameters are reported.

d. Darunavir administered with HOLKIRA™ PAK in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.

e. 0.5 mg sirolimus was administered with ombitasvir/paritaprevir/ritonavir plus dasabuvir in the test arm and 2 mg sirolimus was administered in the reference arm without ombitasvir/paritaprevir/ritonavir plus dasabuvir.

f. C_{12}: concentration at 12 hours following single dose of everolimus.

g. 30 mg cyclosporine was administered with ombitasvir/paritaprevir/ritonavir plus dasabuvir in the test arm and 100 mg cyclosporine was administered in the reference arm without ombitasvir/paritaprevir/ritonavir plus dasabuvir.

Drug-Food Interactions

Food increased the exposure (AUC) of paritaprevir, ombitasvir, ritonavir, and dasabuvir by up to 211%, 82%, 49%, and 30% respectively relative to the fasting state. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content. (approximately 600 Kcal versus approximately 1000 Kcal). To maximize absorption, HOLKIRA PAK should be taken with food without regard to fat or calorie content (see **DOSAGE AND ADMINISTRATION**).

Drug-Herb Interactions

Co-administration of St. John's wort *(Hypericum perforatum)*, a potent hepatic and intestinal CYP3A4 and/or P-gp inducer, may decrease HOLKIRA PAK plasma concentrations, which may result in loss of therapeutic effect.

St. John's wort *(Hypericum perforatum)* is contraindicated with HOLKIRA PAK (see **CONTRAINDICATIONS**).

Drug-Laboratory Interactions

Interactions of HOLKIRA PAK with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) is ombitasvir/paritaprevir/ritonavir fixed dose combination tablets copackaged with dasabuvir tablets. Ombitasvir/paritaprevir/ritonavir tablets must be administered with dasabuvir tablets.
- HOLKIRA PAK is used in combination with ribavirin in patients with genotype 1a infection. HOLKIRA PAK is used without ribavirin in patients with genotype 1b infection (see **Table 10**).
- Prior to initiation of therapy, assess for laboratory and clinical evidence of hepatic decompensation (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).
- Prior to initiation of therapy, HBV screening should be performed in all patients to decrease the risk of HBV reactivation in patients co-infected with HBV.

Recommended Dose and Dosage Adjustment

The recommended oral dose of HOLKIRA PAK is two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening). HOLKIRA PAK is used in combination with ribavirin in certain patient populations (see **Table 10**).

As a fixed dose combination formulation, no dosage adjustments for HOLKIRA PAK are possible.

HOLKIRA PAK tablets should be swallowed whole, with water if required, and not chewed, broken, or crushed. To maximize absorption, HOLKIRA PAK should be taken with food without regard to fat or calorie content (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption,** *Effects of Food on Oral Absorption*).

Table 10 shows the recommended treatment regimen and duration based on patient population.

Table 10. Treatment Regimen and Duration by Patient Population

Patient Population	HCV Genotype and Subtype	Treatment	Duration
HCV mono-infected subjects **Or** **HCV patients co-infected with HIV**	**Genotype 1a, without cirrhosis or with compensated cirrhosis**	HOLKIRA PAK + ribavirin	12 weeks
	Genotype 1b, without cirrhosis or with compensated cirrhosis	HOLKIRA PAK	12 weeks
Liver transplant recipients: Only patients with normal hepatic function and Metavir fibrosis score ≤ 2	**HCV Genotype 1 regardless of the subtype 1a or 1b**	HOLKIRA PAK + ribavirin	24 weeks
HCV genotype 1a with cirrhosis and with previous null response to pegylated interferon (pegIFN) and ribavirin	**Genotype 1a**	HOLKIRA PAK + ribavirin	24 weeks

Note: HOLKIRA PAK with ribavirin is recommended in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

For specific dosage instructions for ribavirin, including dose modification, refer to the ribavirin Product Monograph.

HOLKIRA PAK should be taken as directed for the prescribed duration, without interruption or dose modification. If HOLKIRA PAK is used in combination with ribavirin, ribavirin should be administered for the same duration as HOLKIRA PAK.

Special Populations

Pediatrics (< 18 years of age)

Safety and effectiveness of HOLKIRA PAK in children less than 18 years of age have not been established.

Geriatrics (≥ 65 years of age)

No dose adjustment of HOLKIRA PAK is warranted in geriatric patients (see **INDICATIONS AND CLINICAL USE; WARNINGS AND PRECAUTIONS, Geriatric Use; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

HCV-HIV-1 Co-infection

For patients with HCV-HIV-1 co-infection, follow the dosage recommendations in **Table 10**. Refer to **DRUG INTERACTIONS** for dosage recommendations for concomitant HIV-1 antiviral drugs.

Liver Transplant Recipients

HOLKIRA PAK in combination with ribavirin is recommended for 24 weeks in liver transplant recipients. Lower ribavirin dose at initiation may be appropriate. In the post liver transplant study, ribavirin dosing was individualized and most patients received 600 to 800 mg per day (see **CLINICAL TRIALS**). For dosing recommendations with calcineurin inhibitors refer to **DRUG INTERACTIONS**.

Hepatic Impairment

No dose adjustment of HOLKIRA PAK is required in patients with mild hepatic impairment (Child-Pugh A). HOLKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Renal Impairment

No dose adjustment of HOLKIRA PAK is required in patients with mild, moderate or severe renal impairment (see **WARNINGS AND PRECAUTIONS, Renal and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**)

Missed Dose

Patients should be informed that in case a dose of ombitasvir/paritaprevir/ritonavir is missed, the prescribed dose can be taken within 12 hours of the scheduled time for the dose that was missed.

In case a dose of dasabuvir is missed, the prescribed dose can be taken within 6 hours of the scheduled time for the dose that was missed.

If more than 12 hours has passed since ombitasvir/paritaprevir/ritonavir is usually taken or more than 6 hours has passed since dasabuvir is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The highest documented single dose administered to healthy subjects was 350 mg for ombitasvir, 400 mg for paritaprevir (with 100 mg ritonavir), 200 mg for ritonavir (with 100 mg paritaprevir), and 2000 mg for dasabuvir. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately. ECG monitoring is recommended.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) combines three direct-acting hepatitis C virus antiviral agents with distinct mechanisms of action, and non-overlapping resistance profiles, to target HCV at multiple steps in the viral lifecycle (see **MICROBIOLOGY, Mechanism of Action**).

Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. Ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication. Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome. The stopping of viral replication leads to a rapid decline of HCV viral load and clearing of HCV levels in the body.

Ritonavir is not active against HCV. Ritonavir is a pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (i.e., area under the curve).

Pharmacodynamics

Effects on Electrocardiogram

In a double blind, placebo and active-controlled (moxifloxacin 400 mg) 4-way crossover thorough QT study in 60 healthy subjects, a single dose of paritaprevir/ritonavir/ombitasvir 200/150/25 mg co-administered with dasabuvir 250 mg resulted in statistically significant QTcF prolongation from 3 to 8 hours post-dosing, with a maximum mean difference from placebo of 3.6 msec (90% CI 1.8, 5.4) at 5 hours. A single dose of paritaprevir/ritonavir/ombitasvir 350/150/50 mg co-administered with dasabuvir 500 mg (providing concentrations approximately 1.8, 6 and 2 times the therapeutic concentrations of ombitasvir, paritaprevir and dasabuvir) resulted in statistically significant QTcF prolongation from 3 to 8 hours post-dosing, with a maximum mean difference from placebo of 5.9 msec (90% CI 4.1, 7.7) at 5 hours. These combination treatments had no noteworthy effect on the QRS duration, the PR interval, or heart rate.

Pharmacokinetics

The pharmacokinetic properties of the combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. **Table 11** shows mean C_{max} and AUC of ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily with dasabuvir 250 mg twice daily following multiple doses with food in healthy subjects.

Table 11. Geometric Mean C_{max}, C_{trough}, AUC of Multiple Doses of Ombitasvir/Paritaprevir/Ritonavir 25/150/100 mg Once Daily with Dasabuvir 250 mg Twice Daily with Food in HCV-Infected Patients and Healthy Subjects

Compound/Population	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC (ng*hr/mL)
HCV-Infected Patients[a]			
Ombitasvir	68	24	1000
Paritaprevir	262	22	2220
Dasabuvir	667	74	3240
Ritonavir	682	35	6180
Healthy Subjects[b]			
Ombitasvir	127	29	1420
Paritaprevir	1470	20	6990
Dasabuvir	1030	269	6840
Ritonavir	1600	33	9470

a. median values

b. geometric mean values

Absorption

Ombitasvir/paritaprevir/ritonavir and dasabuvir were absorbed after oral administration with mean T_{max} of approximately 4 to 5 hours. While ombitasvir and dasabuvir exposures increased in a dose proportional manner, paritaprevir and ritonavir exposures increased in a more than dose proportional manner. Accumulation is minimal for ombitasvir and dasabuvir and approximately 1.5- to 2-fold for ritonavir and paritaprevir. Pharmacokinetic steady state for the combination is achieved after approximately 12 days of dosing.

The absolute bioavailability of ombitasvir and paritaprevir when administered with ritonavir as 25/150/100 mg ombitasvir/paritaprevir/ritonavir was approximately 48% and 53%, respectively. The absolute bioavailability of dasabuvir when administered alone is estimated to be approximately 70%.

Effects of Food on Oral Absorption

Food increased the exposure (AUC) of ombitasvir, paritaprevir, ritonavir, and dasabuvir by up to 82, 211, 49, and 30% respectively relative to the fasting state. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal).

Distribution

Ombitasvir, paritaprevir, ritonavir and dasabuvir are highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood to plasma concentration ratios in humans were 0.49, 0.7, 0.6, and 0.7 for ombitasvir, paritaprevir, ritonavir and dasabuvir, indicating that preferential distribution in the plasma compartment of whole blood.

Ombitasvir

Ombitasvir was approximately 99.9% bound to human plasma proteins over a concentration range of 0.09 to 9 mcg per mL.

Paritaprevir

Paritaprevir was approximately 97 to 98.6% bound to human plasma proteins over a concentration range of 0.08 to 8 mcg per mL.

Ritonavir

Ritonavir was greater than 99% bound to human plasma proteins over a concentration range of 0.007 to 22 mcg per mL.

Dasabuvir

Dasabuvir was greater than 99.5% bound to human plasma proteins over a concentration range of 0.15 to 5 mcg per mL.

In animals, paritaprevir liver levels are significantly higher than plasma levels (e.g. liver: plasma ratio of greater than 300:1 in mouse). *In vitro* data indicate that paritaprevir is a substrate for the human hepatic uptake transporters, OATP1B1 and OATP1B3.

Metabolism

Ombitasvir

Ombitasvir is metabolized via amide hydrolysis followed by oxidative metabolism. Following a 25 mg single dose of ^{14}C-ombitasvir given alone, unchanged parent drug accounted for 8.9% of total radioactivity in human plasma; a total of 13 metabolites were identified in human plasma. These metabolites are not expected to have antiviral activity or off-target pharmacologic activity.

Paritaprevir

Paritaprevir is metabolized predominantly by CYP3A4 and to a lesser extent CYP3A5. Following administration of a single 200/100 mg oral dose of ^{14}C-paritaprevir/ritonavir to humans, the parent drug was the major circulating component accounting for approximately 90% of the plasma radioactivity. At least 5 minor metabolites of paritaprevir have been identified in circulation that accounted for approximately 10% of plasma radioactivity. These metabolites are not expected to have antiviral activity.

Dasabuvir

Dasabuvir is predominantly metabolized by CYP2C8 and to a lesser extent by CYP3A. Following a 400 mg ^{14}C-dasabuvir dose in humans, unchanged dasabuvir was the major component (approximately 60%) of drug related radioactivity in plasma; seven metabolites were identified in plasma. The most abundant plasma metabolite was M1, which represented 21% of drug-related radioactivity (AUC) in circulation and has similar activity (after correction for plasma protein binding) as the parent drug against genotype 1 *in vitro*.

Ritonavir

Ritonavir is predominantly metabolized by CYP3A and to a lesser extent, by CYP2D6. Nearly the entire plasma radioactivity after a single 600 mg dose of ^{14}C-ritonavir oral solution in humans was attributed to unchanged ritonavir.

Excretion

Ombitasvir

Following dosing of ombitasvir/paritaprevir/ritonavir with or without dasabuvir, mean plasma half-life of ombitasvir was approximately 21 to 25 hours. Following a 25 mg ^{14}C-ombitasvir dose, approximately 90.2% of the radioactivity was recovered in feces with limited radioactivity (1.91%) in urine. Unchanged ombitasvir accounted for 87.8% of the radioactivity in the feces and 0.03% in the urine.

Paritaprevir

Following dosing of ombitasvir/paritaprevir/ritonavir with or without dasabuvir, mean plasma half-life of paritaprevir was approximately 5.5 hours. Following a 200 mg ^{14}C-paritaprevir dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in feces with limited radioactivity (8.8%) in urine. Unchanged paritaprevir accounted for 1.1% of the radioactivity in the feces and 0.05% in the urine. Unchanged parent drug and M29, the product of fecal hydrolysis, accounted for 87.8% of total radioactivity recovered in feces, indicating that biliary excretion of parent drug is a major elimination pathway for paritaprevir.

Dasabuvir

Following dosing of dasabuvir with ombitasvir/paritaprevir/ritonavir, mean plasma half-life of dasabuvir was approximately 5.5 to 6 hours. Following a 400 mg ^{14}C-dasabuvir dose, approximately 94.4% of the radioactivity was recovered in feces with limited radioactivity (approximately 2%) in urine. Unchanged dasabuvir accounted for 26% of the radioactivity in the feces and 0.03% in the urine.

Ritonavir

Following dosing of paritaprevir/ritonavir/ombitasvir, mean plasma half-life of ritonavir was approximately 4 hours. Following a 600 mg dose of ^{14}C-ritonavir oral solution, 86.4% of the radioactivity was recovered in the feces and 11.3% of the dose was excreted in the urine.

Special Populations and Conditions

Pediatrics

The pharmacokinetics of HOLKIRA PAK in pediatric patients has not been established (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (< 18 years of age)**).

Geriatrics (> 65 years of age)

Population pharmacokinetic analysis of data from Phase 3 clinical studies with HOLKIRA PAK showed that a 10 year increase or decrease in age from 54 years (median age in the Phase 3 studies) would result in approximately 10% change in ombitasvir exposures, ≤ 20% change in paritaprevir exposures and < 10% change in dasabuvir exposures. Age was not a significant predictor for ritonavir exposures. There is no pharmacokinetic information in patients > 75 years. Phase 3 studies of HOLKIRA PAK included 174 patients aged 65 and over. The response rates observed for patients ≥ 65 years of age (97%) were similar to those of patients < 65 years of age (96%), across treatment groups (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (> 65 years of age)**.

Gender

Population pharmacokinetic analysis of data from Phase 3 clinical studies with HOLKIRA PAK showed that female patients would have approximately 55% higher ombitasvir exposures, 100% higher paritaprevir exposures, 15% higher ritonavir exposures and 14 to 30% higher dasabuvir exposures than male patients. The relationship between gender and HOLKIRA PAK exposures was not considered clinically relevant as high response rates (SVR > 90%) were achieved in male and female patients across the Phase 3 studies.

Race

Based on population pharmacokinetic analyses, exposures of ombitasvir, paritaprevir, dasabuvir and ritonavir were not significantly different in patients of Black race compared to patients of other races. Population pharmacokinetic analysis of data from Phase 3 clinical studies with

HOLKIRA PAK showed that Asian patients had 18 to 21% higher ombitasvir exposures, 37 to 39% higher paritaprevir exposures and 29 to 39% higher dasabuvir exposures than non-Asian patients. The ritonavir exposures were comparable between Asians and non-Asians. These differences in exposures were not clinically significant.

Hepatic Insufficiency

The single dose pharmacokinetics of the combination of paritaprevir 200 mg, ritonavir 100 mg, ombitasvir 25 mg, and dasabuvir 400 mg were evaluated in healthy subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment.

In patients with mild hepatic impairment, ombitasvir, paritaprevir and ritonavir mean AUC values decreased by 8, 29 and 34%, respectively, and dasabuvir mean AUC values were 17% higher compared to patients with normal hepatic function. No dose adjustment for HOLKIRA PAK is recommended for HCV-infected patients with mild hepatic impairment.

In patients with moderate hepatic impairment, ombitasvir and ritonavir mean AUC values decreased by 30%, paritaprevir mean AUC value increased by 62% and dasabuvir mean AUC values were 16 % lower compared to patients with normal hepatic function. HOLKIRA PAK is contraindicated in patients with moderate hepatic impairment (Child Pugh B) (see **WARNINGS AND PRECAUTIONS** and **CONTRAINDICATIONS**).

In patients with severe hepatic impairment, paritaprevir and dasabuvir mean AUC values increased by 945% and 325%, respectively, ritonavir mean AUC value was 13% higher, and ombitasvir mean AUC value decreased by 54% compared to patients with normal hepatic function. HOLKIRA PAK is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see **CONTRAINDICATIONS**).

Renal Insufficiency

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 150 mg and ritonavir 100 mg, with or without dasabuvir 400 mg were evaluated in patients with mild (creatinine clearance [CrCl]: 60 to 89 mL per min), moderate (CrCl: 30 to 59 mL per min) and severe (CrCl: 15 to 29 mL per min) renal impairment.

In patients with mild renal impairment, the mean AUC values of ombitasvir, paritaprevir, ritonavir and dasabuvir were < 1, 19, 42, and 21% higher, respectively, compared to subjects with normal renal function.

In patients with moderate renal impairment, the mean AUC values of ombitasvir, paritaprevir, ritonavir and dasabuvir were < 1, 33, 80, and 37% higher, respectively, compared to subjects with normal renal function.

In patients with severe renal impairment, the mean AUC values of ombitasvir, paritaprevir, ritonavir and dasabuvir were < 1, 45, 114, and 50% higher, respectively, compared to subjects with normal renal function.

Consult the ribavirin Product Monograph for patients with renal impairment.

STORAGE AND STABILITY

Store between 2 and 30°C. Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) is ombitasvir/paritaprevir/ritonavir fixed dose combination tablets co-packaged with dasabuvir tablets.

- Ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with "AV1" on one side.
- Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with "AV2" on one side.

HOLKIRA PAK is dispensed in a convenient monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs.

Each daily dose pack contains four tablets: two 12.5/75/50 mg ombitasvir/paritaprevir/ritonavir tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening.

Listing of Non-Medicinal Ingredients

Each ombitasvir/paritaprevir/ritonavir fixed dose combination tablet contains 12.5 mg ombitasvir /75 mg paritaprevir/50 mg ritonavir with the following non-medicinal ingredients: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, propylene glycol monolaurate, sodium stearyl fumarate, sorbitan monolaurate, and vitamin E polyethylene glycol succinate. The film-coating ingredients include: iron oxide red, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide. The tablets do not contain gluten.

Each dasabuvir immediate release tablet contains 250 mg dasabuvir (as dasabuvir sodium monohydrate) with the following non-medicinal ingredients: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose. The film-coating ingredients include: iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide. The tablets do not contain gluten.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

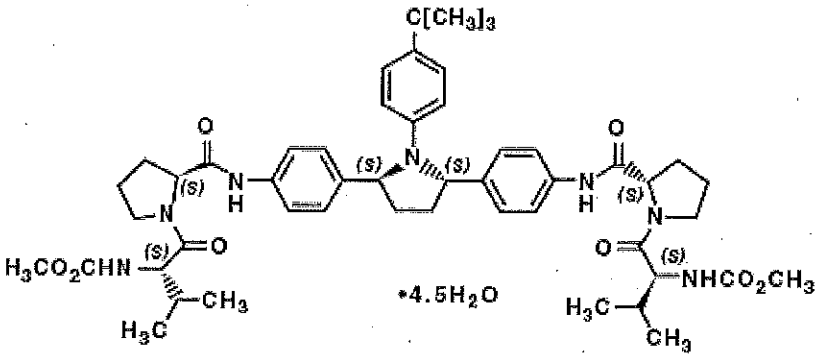
Ombitasvir Hydrate

Common name: ombitasvir

Chemical name: Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate

Molecular formula and molecular mass: $C_{50}H_{67}N_7O_8 \cdot 4.5H_2O$ (hydrate) 975.20 (hydrate)

Structural formula:

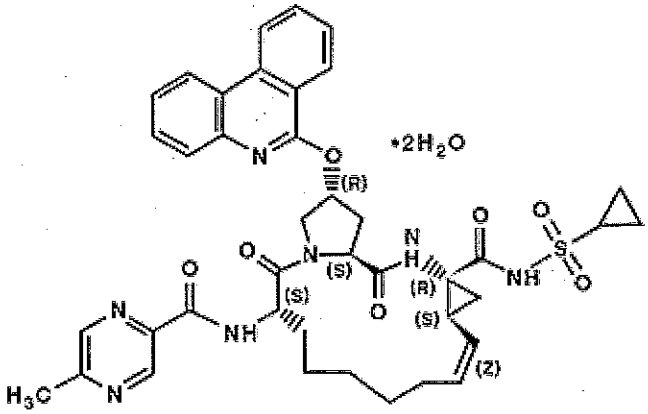


Physicochemical properties:

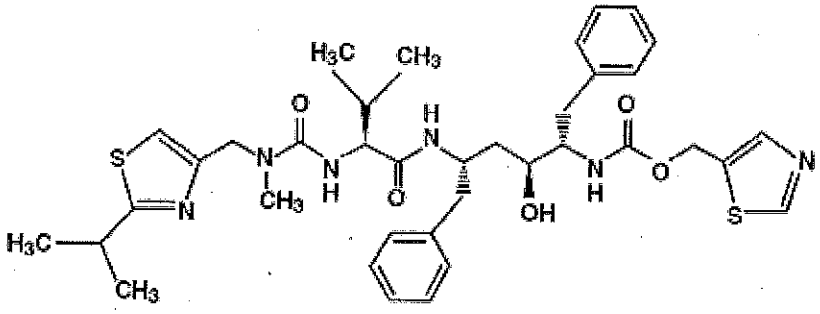
Appearance: Ombitasvir Hydrate is a white to light yellow to light pink powder.

Solubility: Ombitasvir Hydrate is practically insoluble in aqueous buffers but is soluble in ethanol.

Paritaprevir Hydrate

Common name:	paritaprevir
Chemical name:	(2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate
Molecular formula and molecular mass:	$C_{40}H_{43}N_7O_7S \cdot 2H_2O$ (dihydrate) 801.91 (dihydrate)
Structural formula:	
Physicochemical properties:	
Appearance	Paritaprevir Hydrate is a white to off white powder.
Solubility	Paritaprevir Hydrate has very low water solubility.

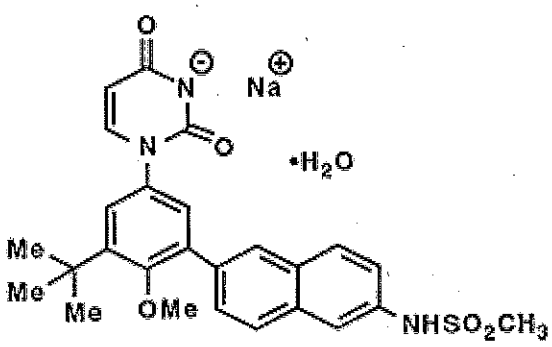
Ritonavir

Proper name:	ritonavir
Chemical name:	[5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methyethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester
Molecular formula and molecular mass:	$C_{37}H_{48}N_6O_5S_2$ 720.95
Structural formula:	

Physicochemical properties:

Appearance	Ritonavir is a white to off white to light tan powder.
Solubility	Ritonavir is insoluble in water and freely soluble in methanol and ethanol.

Dasabuvir

Common name:	dasabuvir sodium monohydrate	
Chemical name:	Sodium 3-(3-*tert*-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)	
Molecular formula and molecular mass:	$C_{26}H_{26}N_3O_5S•Na•H_2O$ (monosodium, monohydrate)	533.57 (monosodium, monohydrate)
	$C_{26}H_{27}N_3O_5S$ (free acid, anhydrate)	493.57 (free acid, anhydrate)
Structural formula:		

Physicochemical properties:

Appearance	Dasabuvir is white to pale yellow to pink powder.
Solubility	Dasabuvir is slightly soluble in water and very slightly soluble in methanol and isopropyl alcohol.

CLINICAL TRIALS

Trial Design

The efficacy and safety of HOLKIRA PAK was evaluated in seven Phase 3 clinical trials, including two trials exclusively in patients with cirrhosis (Child-Pugh A), in over 2,300 patients with genotype 1 chronic hepatitis C infection, as summarized in **Table 12.** HOLKIRA PAK was also evaluated in patients with HCV GT1 co-infected with HIV-1 and in HCV GT1-infected liver transplant recipients.

Table 12. Summary of Clinical Trial Designs in Treatment of Genotype 1 Chronic Hepatitis C Infection

Study #	Number of Patients Treated[a]	HCV Genotype (GT)	Trial Design	Dosage, Route of Administration and Duration[b]
Treatment-Naïve[c], without Cirrhosis				
SAPPHIRE-I (M11-646)	631	GT1	Double-blind, randomized, placebo controlled	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg or placebo QD; dasabuvir tablet: 250 mg or placebo BID; RBV tablet: 1,000 or 1,200 mg or placebo QD (divided BID); Oral 12 weeks
PEARL-III (M13-961)	419	GT1b	Double-blind, randomized (RBV or RBV placebo)	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1,000 to 1,200 mg or placebo QD (divided BID); Oral 12 weeks
PEARL-IV (M14-002)	305	GT1a	Double-blind, randomized (RBV or RBV placebo)	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1,000 to 1,200 mg or placebo QD (divided BID) Oral 12 weeks

Study #	Number of Patients Treated[a]	HCV Genotype (GT)	Trial Design	Dosage, Route of Administration and Duration[b]
Treatment-Experienced[d], without Cirrhosis				
SAPPHIRE-II (M13-098)	394	GT1	Double-blind, randomized, placebo controlled	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg or placebo QD; dasabuvir tablet: 250 mg or placebo BID; RBV tablet: 1,000 or 1,200 mg or placebo QD (divided BID) Oral 12 weeks
PEARL-II (M13-389)	179	GT1b	Open-label, randomized (with or without RBV)	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1,000 or 1,200 mg QD (divided BID) Oral 12 weeks
Treatment-Naïve and Treatment-Experienced[d], with Cirrhosis				
TURQUOISE-II (M13-099)	380	GT1	Open-label, randomized to 12 or 24 weeks	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1,000 to 1,200 mg or placebo QD (divided BID) Oral 12 or 24 weeks
TURQUOISE-III (M14-490)	60	GT1b	Open-label	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; Oral 12 weeks
Patients with HCV GT1 Infection-HIV-1 Co-infection				
TURQUOISE-I (M14-004)	63	GT1	Open-label, randomized to 12 or 24 weeks	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1,000 to 1,200 mg QD (divided BID) Oral 12 or 24 weeks

Study #	Number of Patients Treated[a]	HCV Genotype (GT)	Trial Design	Dosage, Route of Administration and Duration[b]
Liver Transplant Recipients				
CORAL-I (M12-999)	34	GT1	Open-label	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet[e]: 600 to 800 mg Oral 24 weeks

BID = twice daily, QD = daily, pegIFN = pegylated interferon, RBV = ribavirin

a. Treated is defined as patients who were randomized and received at least one dose of HOLKIRA PAK.

b. For patients who received ribavirin, the ribavirin dose was 1000 mg per day for patients weighing less than 75 kg or 1200 mg per day for patients weighing greater than or equal to 75 kg.

c. Treatment naïve was defined as not having received any prior therapy for HCV infection.

d. Treatment-experienced patients were defined as either: prior relapsers (patients with HCV RNA undetectable at or after the end of at least 36 weeks of pegIFN/RBV treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up) or prior partial responders (received at least 20 weeks of pegIFN/RBV and achieved a greater than or equal to 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment) or prior null-responders (received at least 12 weeks of pegIFN/RBV treatment and failed to achieve a 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 or, for SAPPHIRE-II and TURQUOISE-II, received at least 4 weeks of pegIFN/RBV treatment and achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at week 4). TURQUOISE-III also enrolled less well characterized failures of pegIFN/RBV treatment.

e. Ribavirin dosing was managed at the discretion of the investigator with 600 to 800 mg per day being the most frequently selected starting doses.

Sustained virologic response (SVR) (virologic cure) was defined as unquantifiable or undetectable HCV RNA 12 weeks after the end of treatment (SVR12) in the Phase 3 trials. Treatment duration was fixed in each trial and was not guided by patients' HCV RNA levels (no response guided algorithm). Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL.

Clinical Trials in Treatment-Naïve Adults

SAPPHIRE-I was a randomized, global, multicenter, double-blind, placebo-controlled trial conducted in 631 treatment-naïve adults with genotype 1 chronic hepatitis C virus infection without cirrhosis. HOLKIRA PAK was given for 12 weeks of treatment in combination with ribavirin (RBV). Patients randomized to the placebo arm received placebo for 12 weeks, after which they received open-label HOLKIRA PAK in combination with ribavirin for 12 weeks.

PEARL-III and PEARL-IV were randomized, global, multicenter, double-blind, controlled trials conducted in 419 treatment-naïve adults with genotype 1b chronic hepatitis C virus infection without cirrhosis (PEARL-III) and 305 treatment-naïve adults with genotype 1a chronic hepatitis C virus infection without cirrhosis (PEARL-IV). Patients were randomized, in a 1:1 ratio (PEARL-III) or a 1:2 ratio (PEARL-IV), to receive HOLKIRA PAK with or without ribavirin for 12 weeks of treatment.

Demographic and baseline characteristics for treatment-naïve patients in SAPPHIRE-I, PEARL-III and PEARL-IV are provided in **Table 13.**

Table 13. Demographic and Baseline Characteristics of Treatment-Naïve Patients without Cirrhosis in SAPPHIRE-I, PEARL-III and PEARL-IV

Characteristics	SAPPHIRE-I N=631	PEARL-III N=419	PEARL-IV N=305
Age (years)			
Median (range)	52 (18 – 70)	50 (19 – 70)	54 (19 – 70)
Gender, n (%)			
Male	344 (54.5)	192 (45.8)	199 (65.2)
Female	287 (45.5)	227 (54.2)	106 (34.8)
Race, n (%)			
White	572 (90.6)	394 (94.3)	257 (84.3)
Black or African American	34 (5.4)	20 (4.8)	36 (11.8)
Asian	14 (2.2)	2 (0.5)	4 (1.3)
Other	11 (1.7)	2 (0.5)	8 (2.6)
Ethnicity, n (%)			
Hispanic or Latino	32 (5.1)	7 (1.7)	28 (9.2)
None of the above	599 (94.9)	412 (98.3)	277 (90.8)
Body mass index, n (%)			
< 30 kg/m^2	529 (83.8)	350 (83.5)	245 (80.3)
≥ 30 kg/m^2	102 (16.2)	69 (16.5)	60 (19.7)
HCV genotype, n (%)			
1a	427 (67.7)	N/A	304 (99.7)
1b	204 (32.3)	419 (100)	1 (0.3)
Baseline HCV RNA			
Mean ± SD ($\log_{10}$ IU/mL)	6.42 ± 0.63	6.31 ± 0.72	6.57 ± 0.63
$<$ 800000 IU/mL, n (%)	132 (20.9)	112 (26.7)	41 (13.4)
$\geq$ 800000 IU/mL, n (%)	499 (79.1)	307 (73.3)	264 (86.6)
IL28B, n (%)			
CC	194 (30.7)	88 (21.0)	94 (30.8)
Non-CC	437 (69.3)	331 (79.0)	211 (69.2)

Characteristics	SAPPHIRE-I N=631	PEARL-III N=419	PEARL-IV N=305
Baseline fibrosis stage, n (%)			
F0-F1	479 (75.9)	291 (69.6)	195 (63.9)
F2	97 (15.4)	85 (20.3)	56 (18.4)
≥ F3	55 (8.7)	42 (10.0)	54 (17.7)
History of depression or bipolar disorder, n (%)			
No	535 (84.8)	380 (90.7)	242 (79.3)
Yes	96 (15.2)	39 (9.3)	63 (20.7)

N/A = Not Applicable.

Study Results

Table 14 shows the SVR12 rates for genotype 1-infected, treatment-naïve patients receiving HOLKIRA PAK with or without ribavirin for 12 weeks in SAPPHIRE-I, PEARL-III and PEARL-IV. All treatment groups met the primary efficacy endpoint. In study PEARL-III, HOLKIRA PAK without ribavirin had similar SVR12 rates (100%) compared to HOLKIRA PAK with ribavirin (99.5%). In study PEARL-IV, HOLKIRA PAK without ribavirin did not meet the pre-specified criteria for non-inferiority to HOLKIRA PAK with ribavirin.

Table 14. **SVR12 for Genotype 1-Infected Treatment-Naïve Patients without Cirrhosis in SAPPHIRE-I, PEARL-III and PEARL-IV**

Treatment Outcome	SAPPHIRE-I Genotype 1	PEARL-III Genotype 1b		PEARL-IV Genotype 1a	
	HOLKIRA PAK + RBV N=473 % (n/N)	HOLKIRA PAK + RBV N=210 % (n/N)	HOLKIRA PAK* N=209 % (n/N)	HOLKIRA PAK + RBV** N=100 % (n/N)	HOLKIRA PAK N=205 % (n/N)
Overall SVR12	96 (456/473)	99 (209/210)	100 (209/209)	97 (97/100)	90 (185/205)
95% CI	94.7 to 98.1	98.6 to 100	98.2 to 100	93.7 to 100	86.2 to 94.3
HCV genotype 1a	96 (308/322)	N/A	N/A	97 (97/100)	90 (184/204)
HCV genotype 1b	98 (148/151)	99 (209/210)	100 (209/209)	N/A	
Outcome for patients without SVR12					
On-treatment VF[a]	<1 (1/473)[d]	<1 (1/210)	0	1 (1/100)	3 (6/205)
Relapse[b]	2 (7/463)[d]	0	0	1 (1/98)	5 (10/194)
Other[c]	2 (9/473)	0	0 (0/209)	1 (1/100)	2 (4/205)

CI = confidence interval, VF = virologic failure, N/A = Not Applicable

* For patients with GT1b infection without cirrhosis, HOLKIRA PAK alone for 12 weeks is the recommended regimen.

** For patients with GT1a infection without cirrhosis, HOLKIRA PAK with RBV for 12 weeks is the recommended regimen.

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

d. No patients with HCV genotype 1b infection experienced on-treatment virologic failure and one patient with HCV genotype 1b infection experienced relapse.

Table 15 presents the SVR12 rates by selected subgroups for genotype 1-infected, treatment-naïve patients in studies SAPPHIRE-I, PEARL-III and PEARL-IV.

Table 15. **SVR12 rates for Selected Subgroups of Genotype 1-infected, Treatment-Naïve Patients without Cirrhosis in SAPPHIRE-I, PEARL-III and PEARL-IV**

Treatment Outcome	SAPPHIRE-I Genotype 1	PEARL-III Genotype 1b		PEARL-IV Genotype 1a	
	HOLKIRA PAK + RBV N=473 % (n/N)	HOLKIRA PAK + RBV N=210 % (n/N)	HOLKIRA PAK* N=209 % (n/N)	HOLKIRA PAK + RBV** N=100 % (n/N)	HOLKIRA PAK N=205 % (n/N)
IL28B					
CC	97 (139/144)	100 (44/44)	100 (44/44)	100 (31/31)	97 (61/63)
Non-CC	96 (317/329)	99 (165/166)	100 (165/165)	96 (66/69)	87 (124/142)
Sex					
Female	98 (197/202)	99 (103/104)	100 (123/123)	100 (30/30)	95 (72/76)
Male	96 (259/271)	100 (106/106)	100 (86/86)	96 (67/70)	88 (113/129)
Age					
< 65 years	97 (438/454)	99 (195/196)	100 (190/190)	97 (87/90)	90 (172/192)
≥ 65 years	95 (18/19)	100 (14/14)	100 (19/19)	100 (10/10)	100 (13/13)
Race					
Black	96 (27/28)	100 (11/11)	100 (11/11)	100 (10/10)	85 (23/27)
Non-black	96 (429/445)	99 (198/199)	100 (197/197)	97 (87/90)	91 (162/178)
Ethnicity					
Hispanic or Latino	93 (25/27)	100 (2/2)	100 (5/5)	90 (9/10)	89 (16/18)
None of the above	97 (431/446)	99 (207/208)	100 (204/204)	98 (88/90)	90 (169/187)
Body mass index					
< 30 kg/m^2	97 (390/402)	100 (182/182)	100 (168/168)	99 (78/79)	92 (153/166)
≥ 30 kg/m^2	92 (65/71)	96 (27/28)	100 (41/41)	90 (19/21)	82 (32/39)
Baseline HCV RNA					
< 800000 IU/mL	98 (102/104)	100 (51/51)	100 (61/61)	100 (8/8)	91 (30/33)
≥ 800000 IU/mL	96 (354/369)	99 (158/159)	100 (148/148)	97 (89/92)	90 (155/172)
Baseline fibrosis stage					
F0-F1	97 (353/363)	99 (149/150)	100 (141/141)	97 (61/63)	92 (122/132)
F2	94 (66/70)	100 (38/38)	100 (47/47)	95 (20/21)	83 (29/35)
≥ F3	93 (37/40)	100 (22/22)	100 (20/20)	100 (16/16)	89 (34/38)

Treatment Outcome	SAPPHIRE-I Genotype 1	PEARL-III Genotype 1b		PEARL-IV Genotype 1a	
	HOLKIRA PAK + RBV N=473 % (n/N)	HOLKIRA PAK + RBV N=210 % (n/N)	HOLKIRA PAK* N=209 % (n/N)	HOLKIRA PAK + RBV** N=100 % (n/N)	HOLKIRA PAK N=205 % (n/N)
History of depression or bipolar disorder					
No	97 (390/403)	99 (189/190)	100 (190/190)	96 (80/83)	89 (142/159)
Yes	94 (66/70)	100 (20/20)	100 (19/19)	100 (17/17)	93 (43/46)

* For patients with GT1b infection without cirrhosis, HOLKIRA PAK alone for 12 weeks is the recommended regimen.

** For patients with GT1a infection without cirrhosis, HOLKIRA PAK with RBV for 12 weeks is the recommended regimen.

These baseline viral (genotype 1 subtype, baseline viral load) and host factors (gender, race, ethnicity, age, IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage) were not associated with lower SVR12 rates across subgroups.

In addition, patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

Clinical Trials in Treatment-Experienced Adults

SAPPHIRE-II was a randomized, global multicenter, double-blind, placebo-controlled trial conducted in 394 patients with genotype 1 chronic hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment with peginterferon and ribavirin (pegIFN/RBV). HOLKIRA PAK in combination with ribavirin was given for 12 weeks of treatment. Patients randomized to the placebo arm received placebo for 12 weeks, after which they received HOLKIRA PAK in combination with ribavirin for 12 weeks.

PEARL-II was a randomized, global, multicenter, open-label trial conducted in 179 adults with chronic genotype 1b hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment with pegIFN/RBV. Patients were randomized, in a 1:1 ratio, to receive HOLKIRA PAK with or without ribavirin for 12 weeks of treatment.

Demographic and baseline characteristics for treatment-experienced patients in SAPPHIRE-II and PEARL-II are provided in **Table 16.**

Table 16. Demographic and Baseline Characteristics of Treatment-Experienced Patients without Cirrhosis in SAPPHIRE-II and PEARL-II

Characteristics	SAPPHIRE-II N=394	PEARL-II N=179
Age (years)		
Median (range)	54 (19 – 71)	57 (26 – 70)
Gender, n (%)		
Male	227 (57.6)	97 (54.2)
Female	167 (42.4)	82 (45.8)
Race, n (%)		
White	355 (90.1)	165 (92.2)
Black or African American	32 (8.1)	7 (3.9)
Asian	6 (1.5)	3 (1.7)
Other	1 (0.3)	4 (2.3)
Ethnicity, n (%)		
Hispanic or Latino	25 (6.3)	3 (1.7)
None of the above	369 (93.7)	176 (98.3)
Body mass index, n (%)		
< 30 kg/m^2	316 (80.2)	140 (78.2)
≥ 30 kg/m^2	78 (19.8)	39 (21.8)
HCV genotype, n (%)		
1a	230 (58.4)	N/A
1b	163 (41.4)	179 (100)
Baseline HCV RNA		
Mean ± SD ($\log_{10}$ IU/mL)	6.55 ± 0.52	6.51 ± 0.55
$<$ 800000 IU/mL, n (%)	51 (12.9)	22 (12.3)
$\geq$ 800000 IU/mL, n (%)	343 (87.1)	157 (87.7)
IL28B, n (%)		
CC	41 (10.4)	17 (9.5)
Non-CC	353 (89.6)	162 (90.5)
Type of response to previous pegIFN/RBV treatment, n (%)		
Null responder	193 (49.0)	63 (35.2)
Nonresponder/partial responder	86 (21,8)	51 (28.5)
Relapser	115 (29.2)	65 (36.3)
Baseline fibrosis stage, n (%)		
F0-F1	267 (67.8)	122 (68.2)
F2	70 (17.8)	32 (17.9)
$\geq$ F3	57 (14.5)	25 (14.0)

Characteristics	SAPPHIRE-II N=394	PEARL-II N=179
History of depression or bipolar disorder, n (%)		
No	313 (79.4)	156 (87.2)
Yes	81 (20.6)	23 (12.8)

N/A = Not Applicable

Study Results

Table 17 shows the SVR12 rates for treatment-experienced patients with genotype 1-infection receiving HOLKIRA PAK in combination with ribavirin for 12 weeks in SAPPHIRE-II and PEARL-II and HOLKIRA PAK alone in PEARL-II. All the treatment groups met the primary efficacy endpoint.

Table 17. SVR12 for Genotype 1-Infected Treatment-Experienced Patients without Cirrhosis in SAPPHIRE-II and PEARL-II

Treatment Outcome	SAPPHIRE-II Genotype 1	PEARL-II Genotype 1b	
	HOLKIRA PAK + RBV N=297 % (n/N)	HOLKIRA PAK + RBV N=88 % (n/N)	HOLKIRA PAK* N=91 % (n/N)
Overall SVR12	96 (286/297)	98 (86/88)	100 (91/91)
95% CI	94.1 to 98.4	94.6 to 100	95.9 to 100
HCV genotype 1a	96 (166/173)	N/A	N/A
Prior pegIFN/RBV null responder	95 (83/87)	N/A	N/A
Prior pegIFN/RBV partial responder	100 (36/36)	N/A	N/A
Prior pegIFN/RBV relapser	94 (47/50)	N/A	N/A
HCV genotype 1b	97 (119/123)	98 (86/88)	100 (91/91)
Prior pegIFN/RBV null responder	95 (56/59)	97 (30/31)	100 (32/32)
Prior pegIFN/RBV partial responder	100 (28/28)	96 (24/25)	100 (26/26)
Prior pegIFN/RBV relapser	97 (35/36)	100 (32/32)	100 (33/33)
Outcome for patients without SVR12			
On-treatment VF[a]	0	0	0
Relapse[b]	2 (7/293)	0	0
Other[c]	1 (4/297)	2 (2/88)	0

Treatment Outcome	SAPPHIRE-II Genotype 1	PEARL-II Genotype 1b	
	HOLKIRA PAK + RBV N=297 % (n/N)	HOLKIRA PAK + RBV N=88 % (n/N)	HOLKIRA PAK* N=91 % (n/N)

CI = confidence interval, VF = virologic failure, N/A = Not Applicable

* For patients with GT1b infection without cirrhosis, HOLKIRA PAK alone for 12 weeks is the recommended regimen.

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Table 18 presents the SVR12 rates by selected subgroups for genotype 1-infected, treatment-experienced patients in studies SAPPHIRE-II and PEARL-II.

Table 18. SVR12 rates for Selected Subgroups of Genotype 1-infected, Treatment-Experienced Patients without Cirrhosis in SAPPHIRE-II and PEARL-II

Treatment Outcome	SAPPHIRE-II Genotype 1	PEARL-II Genotype 1b	
	HOLKIRA PAK + RBV N=297 % (n/N)	HOLKIRA PAK + RBV N=88 % (n/N)	HOLKIRA PAK* N=91 % (n/N)
IL28B			
CC	91 (31/34)	100 (10/10)	100 (7/7)
Non-CC	97 (255/263)	97 (76/78)	100 (84/84)
Sex			
Female	97 (126/130)	98 (44/45)	100 (37/37)
Male	96 (160/167)	98 (42/43)	100 (54/54)
Age			
< 65 years	97 (269/277)	97 (71/73)	100 (76/76)
≥ 65 years	85 (17/20)	100 (15/15)	100 (15/15)
Race			
Black	95 (21/22)	100 (3/3)	100 (5/5)
Non-black	96 (265/275)	98 (83/85)	100 (86/86)
Ethnicity			
Hispanic or Latino	95 (21/22)	50 (1/2)	100 (1/1)
None of the above	96 (265/275)	99 (85/86)	100 (90/90)

Treatment Outcome	SAPPHIRE-II Genotype 1	PEARL-II Genotype 1b	
	HOLKIRA PAK + RBV N=297 % (n/N)	HOLKIRA PAK + RBV N=88 % (n/N)	HOLKIRA PAK* N=91 % (n/N)
Body mass index			
< 30 kg/m^2	97 (231/238)	97 (69/71)	100 (69/69)
≥ 30 kg/m^2	93 (55/59)	100 (17/17)	100 (22/22)
Baseline HCV RNA			
< 800000 IU/mL	100 (42/42)	100 (13/13)	100 (9/9)
≥ 800000 IU/mL	96 (244/255)	97 (73/75)	100 (82/82)
Baseline fibrosis stage			
F0-F1	98 (197/202)	97 (61/63)	100 (59/59)
F2	94 (50/53)	100 (13/13)	100 (19/19)
$\geq$ F3	93 (39/42)	100 (12/12)	100 (13/13)
History of depression or bipolar disorder			
No	96 (220/229)	99 (72/73)	100 (83/83)
Yes	97 (66/68)	93 (14/15)	100 (8/8)

* For patients with GT1b infection without cirrhosis, HOLKIRA PAK alone for 12 weeks is the recommended regimen.

These baseline viral (genotype 1 subtype, baseline viral load) and host factors (prior treatment response, sex, race, ethnicity, age, IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage) were not associated with lower SVR12 rates across subgroups.

In addition, patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

Clinical Trials in Patients with Cirrhosis

TURQUOISE-II was a randomized, global multicenter, open-label trial conducted exclusively in 380 genotype 1-infected patients with cirrhosis (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. HOLKIRA PAK in combination with ribavirin was administered for either 12 or 24 weeks of treatment.

TURQUOISE-III is a Phase 3b, open-label, single-arm, multicenter study evaluating the efficacy and safety of HOLKIRA PAK administered for 12 weeks in HCV genotype 1b-infected, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis.

Demographic and baseline characteristics for genotype 1-infected patients with cirrhosis in studies TURQUOISE-II and TURQUOISE-III are provided in **Table 19**.

Table 19. Demographic and Baseline Characteristics of Patients with Cirrhosis in TURQUOISE-II and TURQUOISE-III

Characteristics	TURQUOISE-II HOLKIRA PAK + RBV N = 380	TURQUOISE-III HOLKIRA PAK N = 60
Age (years)		
Median (range)	58 (21 – 71)	60.5 (26 – 78)
Gender, n (%)		
Male	267 (70.3)	37 (61.7)
Female	113 (29.7)	23 (38.3)
Race, n (%)		
White	360 (94.7)	52 (86.7)
Black or African American	12 (3.2)	7 (11.7)
Asian	8 (2.1)	0
Ethnicity		
Hispanic or Latino	45 (11.8)	3 (5.0)
None of the above	335 (88.2)	57 (95.0)
Body mass index		
< 30 kg/m^2	272 (71.6)	43 (71.7)
≥ 30 kg/m^2	108 (28.4)	17 (28.3)
HCV genotype, n (%)		
1a	261 (68.7)	0
1b	119 (31.3)	60 (100)
Baseline HCV RNA		6.57 (0.6)
Mean ± SD ($\log_{10}$ IU/mL)	6.47 ± 0.58	5 (8.3)
< 800000 IU/mL, n (%)	53 (13.9)	55 (91.7)
≥ 800000 IU/mL, n (%)	327 (86.1)	
Prior HCV Therapy		
Treatment-Naive	160 (42.1)	27 (45.0)
Treatment-experienced with pegIFN/RBV, n (%)	220 (57.9)	33 (55.0)
Null responder	137 (36.1)	7 (21.2)
Partial responder	31 (8.2)	5 (15.2)
Relapser	52 (13.7)	3 (9.1)
Other pegIFN/RBV failures	N/A	18 (54.5)[+]
IL28B, n (%)		
CC	69 (18.2)	10 (16.7)
CT	237 (62.4)	36 (60.0)
TT	74 (19.5)	14 (23.3)

Characteristics	TURQUOISE-II HOLKIRA PAK + RBV N = 380	TURQUOISE-III HOLKIRA PAK N = 60
Baseline platelet count, n (%)		
$< 90 \times 10^9$/L	56 (14.7)	13 (21.7)
$\geq 90 \times 10^9$/L	324 (85.3)	47 (78.3)
Baseline albumin, n (%)		
< 35 g/L	43 (11.3)	10 (16.7)
≥ 35 g/L	337 (88.7)	50 (83.3)
History of depression or bipolar disorder, n (%)		
No	286 (75.3)	43 (71.7)
Yes	94 (24.7)	17 (28.3)

N/A = Not Applicable.

[+] Other types of pegIFN/RBV failure include less well documented non-response, relapse/breakthrough or other pegIFN failure.

Study Results

Table 20 shows the SVR12 rates for genotype 1-infected patients with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV in studies TURQUOISE-II and TURQUOISE-III. All the treatment groups met the primary efficacy endpoint.

Table 20. SVR12 for Genotype 1-Infected Patients with Cirrhosis who were Treatment-Naïve or Previously Treated with pegIFN/RBV in TURQUOISE-II and TURQUOISE-III

Treatment Outcome	TURQUOISE-II HOLKIRA PAK with RBV		TURQUOISE-III HOLKIRA PAK
	12 Weeks*	12 Weeks	12 Weeks
	% (n/N)	% (n/N)	% (n/N)
Overall SVR12	92 (191/208)[d]	97 (166/172)[d]	100 (60/60)
97.5% CI	87.6 to 96.1	93.4 to 99.6	N/A
95% CI	N/A	N/A	94.0 to 100.0
HCV genotype 1a	89 (124/140)	95 (115/121)	N/A
Treatment naïve	92 (59/64)	95 (53/56)	N/A
Prior pegIFN/RBV null responders	80 (40/50)	93 (39/42)**	N/A
Prior pegIFN/RBV partial responders	100 (11/11)	100 (10/10)	N/A
Prior pegIFN/RBV prior relapsers	93 (14/15)	100 (13/13)	N/A
HCV genotype 1b	99 (67/68)	100 (51/51)	100 (60/60)
Treatment naïve	100 (22/22)	100 (18/18)	100 (27/27)

Treatment Outcome	TURQUOISE-II		TURQUOISE-III
	HOLKIRA PAK with RBV		HOLKIRA PAK
	12 Weeks*	12 Weeks	12 Weeks
	% (n/N)	% (n/N)	% (n/N)
Prior pegIFN/RBV null responders	100 (25/25)	100 (20/20)	100 (7/7)
Prior pegIFN/RBV partial responders	86 (6/7)	100 (3/3)	100 (5/5)
Prior pegIFN/RBV prior relapsers	100 (14/14)	100 (10/10)	100 (3/3)
Other pegIFN/RBV failures	N/A	N/A	100 (18/18)[+]
Outcome for patients without SVR12			
On-treatment VF[a]	<1 (1/208)	2 (3/172)	0
Relapse[b]	6 (12/203)	<1 (1/164)	0
Other[c]	2 (4/208)	1 (2/172)	0

CI = confidence interval, VF = virologic failure , N/A = Not Applicable

* 12 weeks of HOLKIRA PAK with RBV is the recommended regimen for all patients with cirrhosis,except those with genotype 1a infection and prior null response to pegIFN/RBV.

**24 weeks of HOLKIRA PAK + ribavirin is recommended for patients with genotype 1a-infection with cirrhosis who have had a previous null response to pegIFN/RBV.

[+] Other types of pegIFN/RBV failure include less well documented non-response, relapse/breakthrough or other pegIFN failure.

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA < 25 IU/mL at last observation during at least 11 or 22 weeks of treatment, for patients assigned to 12 or 24 weeks of treatment, respectively.

c. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Based on logistic regression, the difference between treatment arms was not statistically significant (p value = 0.089).

Table 21 presents the SVR12 rates by selected subgroups for genotype 1-infected patients with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

Table 21. SVR12 rates for Selected Subgroups of Genotype 1-infected Patients with Cirrhosis who were Treatment-Naïve or Previously Treated with pegIFN/RBV in TURQUOISE-II and TRUQUOISE-III

	TURQUOISE-II		TURQUOISE-III
	HOLKIRA PAK + RBV		HOLKIRA PAK
	12 Weeks N = 208	24 Weeks N = 172	12 Weeks N = 60
Subgroup	% (n/N)	% (n/N)	% (n/N)
IL28B			
CC	94 (33/35)	97 (33/34)	100 (10/10)
Non-CC	91 (158/173)	96 (133/138)	100 (50/50)
Sex			
Female	94 (58/62)	98 (50/51)	100 (23/23)
Male	91 (133/146)	96 (116/121)	100 (37/37)
Age			
< 65 years	91 (166/182)	96 (143/149)	100 (45/45)
≥ 65 years	96 (25/26)	100 (23/23)	100 (15/15)
Race			
Black	100 (6/6)	83 (5/6)	100 (7/7)
Nonblack	92 (185/202)	97 (161/166)	100 (53/53)
Ethnicity			
Hispanic or Latino	84 (21/25)	95 (19/20)	100 (3/3)
None of the above	93 (170/183)	97 (147/152)	100 (57/57)
Body mass index			
< 30 kg/m^2	92 (135/146)	98 (123/126)	100 (43/43)
≥ 30 kg/m^2	90 (56/62)	93 (43/46)	100 (17/17)
Baseline HCV RNA			
< 800000 IU/mL	91 (31/34)	89 (17/19)	100 (5/5)
≥ 800000 IU/mL	92 (160/174)	97 (149/153)	100 (55/55)
Baseline platelet count			
< 90 x 10^9/L	83 (25/30)	96 (25/26)	100 (13/13)
≥ 90 x 10^9/L	93 (166/178)	97 (141/146)	100 (47/47)
Baseline albumin			
< 35 g/L	84 (21/25)	89 (16/18)	100 (10/10)
≥ 35 g/L	93 (170/183)	97 (150/154)	100 (50/50)
History of depression or bipolar disorder			
No	91 (143/157)	97 (125/129)	100 (43/43)
Yes	94 (48/51)	95 (41/43)	100 (17/17)

	TURQUOISE-II		TURQUOISE-III
	HOLKIRA PAK + RBV		HOLKIRA PAK
	12 Weeks N = 208	24 Weeks N = 172	12 Weeks N = 60
Subgroup	% (n/N)	% (n/N)	% (n/N)

Patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

Pooled Analyses of Clinical Trials

Durability of Response

Overall, 660 patients in Phase 2 and 3 clinical trials had HCV RNA results for both the SVR12 and SVR24 time points. Among these patients, the positive predictive value of SVR12 on SVR24 was 99.8%.

Pooled Efficacy Analysis

In Phase 3 clinical trials, 1088 patients (including 194 with cirrhosis) received the recommended regimen for their HCV subtype, cirrhosis status and previous treatment. **Table 22** shows SVR rates for these patients. Among patients who received the recommended regimen in Phase 3 clinical trials, 97% achieved SVR (95% with cirrhosis and 97% without cirrhosis), while 0.6% demonstrated virologic breakthrough and 1.5% experienced post-treatment relapse.

Table 22. SVR12 Rates for Recommended Treatment Regimens

	Genotype 1a		Genotype 1b	
	No Cirrhosis HOLKIRA PAK with RBV	With Cirrhosis HOLKIRA PAK with RBV	No Cirrhosis HOLKIRA PAK	With Cirrhosis HOLKIRA PAK
	12 weeks	12 weeks*	12 weeks	12 weeks
Treatment-naïve	96% (403/420)	92% (61/66)	100% (210/210)	100% (27/27)
Treatment-experienced	96% (166/173)	94% (64/68)*	100% (91/91)	100% (33/33)+
Prior pegIFN/RBV relapser	94% (47/50)	93% (14/15)	100% (33/33)	100% (3/3)
Prior pegIFN/RBV partial responder	100% (36/36)	100% (11/11)	100% (26/26)	100% (5/5)
Prior pegIFN/RBV null responder	95% (83/87)	93% (39/42) (24 weeks)	100% (32/32)	100% (7/7)
Other pegIFN/RBV failures	0	0	0	100 % (18/18)+
TOTAL	96% (569/593)	93% (125/134)*	100% (301/301)	100% (60/60)

* All patients received 12 weeks of therapy except for genotype 1a infected prior null responders with cirrhosis who received 24 weeks of therapy.

\+ Other types of pegIFN/RBV failure include less well documented non-response, relapse/breakthrough or other pegIFN failure.

Impact of Ribavirin Dose Adjustment on Probability of SVR

In Phase 3 clinical trials, 91.5% of patients did not require ribavirin dose adjustments during therapy. In the 8.5% of patients who had ribavirin dose adjustments during therapy, the SVR rate (98.5%), was comparable to patients who maintained their starting ribavirin dose throughout treatment.

Clinical Trial in Patients with HCV Genotype 1 Infection-HIV-1 Co-infection (TURQUOISE-I)

In an open-label clinical trial (TURQOISE-I) the safety and efficacy of 12 or 24 weeks of treatment with HOLKIRA PAK and ribavirin was evaluated in 63 patients with genotype 1 chronic hepatitis C co-infected with HIV-1. See **DOSAGE AND ADMINISTRATION** for dosing recommendations in HCV-HIV-1 co-infected patients. Patients were on a stable HIV-1 antiretroviral therapy (ART) regimen that included ritonavir-boosted atazanavir or raltegravir, co-administered with a backbone of tenofovir plus emtricitabine or lamivudine.

Treated patients (N = 63) had a median age of 51 years (range: 31 to 69); 24% of patients were Black; 81% of patients had IL28B non-CC genotype; 19% of patients had compensated cirrhosis; 67% of patients were HCV treatment-naïve; 33% of patients had failed prior treatment with pegIFN/RBV; 89% of patients had HCV genotype 1a infection.

Study Results

Table 23 shows the SVR12 rates for patients with HCV genotype 1 infection and HIV-1 co-infection in TURQUOISE-I.

Table 23. SVR12 for HIV-1 Co-infected Patients in TURQUOISE-I

	Arm A 12 Weeks N = 31	Arm B 24 Weeks N = 32
SVR12, n/N (%) 95% CI	29/31 (93.5) 79.3, 98.2	29/32 (90.6) 75.8, 96.8
Outcome of patients not achieving SVR12		
On-treatment virologic failure[a]	0	1
Post-treatment relapse[b]	1	2[c]
Other[d]	1	0

a. On-treatment virologic failure was defined as confirmed HCV RNA ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

c. These virologic failures appear to have resulted from reinfection based on phylogenetic analyses of baseline and virologic failure samples.

d. Other includes patients not achieving SVR12 but not experiencing on-treatment virologic failure or relapse (e.g., missing HCV RNA values in the SVR12 window).

In TURQUOISE-I, the SVR12 rates in HCV/HIV-1 co-infected patients were consistent with SVR12 rates in the Phase 3 trials of HCV mono-infected patients. Fifty-one of 56 (91.1%) patients with genotype 1a infection and 7 of 7 (100%) patients with genotype 1b infection achieved SVR12. Five of 6 (83.3%) patients with compensated cirrhosis in each arm achieved SVR12.

Clinical Trial in Liver Transplant Recipients (CORAL-I)

The safety and efficacy of HOLKIRA PAK with ribavirin was studied in 34 HCV genotype 1-infected liver transplant recipients who were at least 12 months post transplantation at enrollment. The primary objectives of this study were to assess the safety and the percentage of patients achieving SVR12 following 24 weeks of treatment with HOLKIRA PAK and ribavirin. The initial dose of ribavirin was left to the discretion of the investigator with 600 to 800 mg per day being the most frequently selected dose range at initiation of HOLKIRA PAK and at the end of treatment.

Study Results

Thirty-four patients (29 with HCV genotype 1a infection and 5 with HCV genotype 1b infection) who had not received treatment for HCV infection after transplantation and had a METAVIR fibrosis score of F2 or less were enrolled. Thirty-three out of the 34 patients (97.1%) achieved SVR12 (96.6% in patients with genotype 1a infection and 100% in patients with genotype 1b infection). One patient with HCV genotype 1a infection relapsed post-treatment.

MICROBIOLOGY

Mechanism of Action

HOLKIRA PAK combines three direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication. In replicon cell culture assays, ombitasvir has half maximal effective concentration (EC_{50}) values of 14.1 and 5.0 pM against HCV genotypes 1a and 1b, respectively.

Paritaprevir

Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, paritaprevir inhibited the proteolytic activity of the recombinant HCV genotype 1a and 1b NS3/4A protease enzymes with half maximal inhibitory concentration (IC_{50}) values of 0.18 and 0.43 nM, respectively.

Dasabuvir

Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome. In a biochemical assay, dasabuvir inhibited the polymerase activity of the recombinant HCV genotype 1a and 1b HCV NS5B enzymes with IC_{50} values of 2.8 and 10.7 nM, respectively.

Activity in Cell Culture and/or Biochemical Studies

Ombitasvir

The EC_{50} of ombitasvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays was 14.1 and 5 pM, respectively. The activity of ombitasvir was attenuated 11- to 13-fold in the presence of 40% human plasma. The mean EC_{50} of ombitasvir against replicons containing NS5A from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.66 pM (range 0.35 to 0.88 pM; n = 11) and 1.0 pM (range 0.74 to 1.5 pM; n = 11), respectively. Ombitasvir has EC_{50} values of 12, 4.3, 19, 1.7, 0.38, 3.2, and 366 pM against replicon cell lines constructed with NS5A from single isolates representing genotypes 2a, 2b, 3a, 4a, 4d, 5a, and 6a, respectively.

Paritaprevir

The EC_{50} of paritaprevir against genotype 1a-H77 and 1b-Con1 strains in the HCV replicon cell culture assay was 1.0 and 0.21 nM, respectively. The activity of paritaprevir was attenuated 24- to 27-fold in the presence of 40% human plasma. The mean EC_{50} of paritaprevir against replicons containing NS3 from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.86 nM (range 0.43 to 1.87 nM; n = 11) and 0.06 nM (range 0.03 to 0.09 nM; n = 9), respectively. Paritaprevir had an EC_{50} value of 5.3 nM against the 2a-JFH-1 replicon cell line, and EC_{50} values of 19, 0.09, 0.015, and 0.68 nM against replicon cell lines containing NS3 from a single isolate each of genotype 3a, 4a, 4d, and 6a, respectively. In a biochemical assay, paritaprevir inhibited the activity of NS3/4A enzymes from single isolates of genotypes 2a, 2b, 3a, and 4a with IC_{50} values of 2.4, 6.3, 14.5, and 0.16 nM, respectively. .

Dasabuvir

The EC_{50} of dasabuvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays was 7.7 and 1.8 nM, respectively. The replicon activity of dasabuvir was attenuated 12- to 13-fold in the presence of 40% human plasma. The mean EC_{50} of dasabuvir against replicons containing NS5B from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.77 nM (range 0.4 to 2.1 nM; n = 11) and 0.46 nM (range 0.2 to 2 nM; n = 10), respectively. In biochemical assays, dasabuvir inhibited a panel of genotype 1a and 1b polymerases with a mean IC_{50} value of 4.2 nM (range 2.2 to 10.7 nM; n = 7).

Ritonavir

Ritonavir did not exhibit a direct antiviral effect on the replication of HCV subgenomic replicons, and the presence of ritonavir did not affect the *in vitro* antiviral activity of paritaprevir.

Combination Activity *in vitro*

All two-drug combinations of paritaprevir, ombitasvir, dasabuvir and ribavirin demonstrated additive to synergistic inhibition of HCV genotype 1 replicon at the majority of drug concentrations studied in short term cell culture assays. In long term replicon survival assays, the ability of drug-resistant cells to form colonies in the presence of a single drug or drugs in

combination was evaluated. In pair-wise combinations of paritaprevir, ombitasvir, and dasabuvir at concentrations 10-fold over their respective EC_{50}, colony numbers were reduced by more than 100-fold by two drugs as compared to each drug alone. When all three drugs were combined at concentrations of 5-fold above their respective EC_{50}, no drug-resistant colonies survived.

Resistance in Cell Culture

Resistance to paritaprevir, ombitasvir, or dasabuvir conferred by variants in NS3, NS5A, or NS5B, respectively, selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterized in the appropriate genotype 1a or 1b replicons.

In genotype 1a, substitutions F43L, R155K, A156T, and D168A/H/V/Y in HCV NS3 reduced susceptibility to paritaprevir. In the genotype 1a replicon, the activity of paritaprevir was reduced 20-, 37-, and 17-fold by the F43L, R155K and A156T substitutions, respectively. The activity of paritaprevir was reduced 96-fold by D168V, and 50- to 219-fold by each of the other D168 substitutions. The activity of paritaprevir in genotype 1a was not significantly affected (less than or equal to 3-fold) by single substitutions V36A/M, V55I, Y56H, Q80K or E357K. Double variants including combinations of V36M, Y56H, or E357K with R155K or with a D168 substitution reduced the activity of paritaprevir by an additional 2- to 3-fold relative to the single R155K or D168 substitution. In genotype 1b, substitutions R155Q, D168H, D168V, and Y56H in combination with D168V in HCV NS3 reduced susceptibility to paritaprevir. In the genotype 1b replicon, the activity of paritaprevir was reduced 76- and 159-fold by D168H and D168V, respectively. Y56H alone could not be evaluated due to poor replication capacity, however, the combination of Y56H and D168V reduced the activity of paritaprevir by 2472-fold.

In genotype 1a, substitutions M28T/V, Q30R, H58D, Y93C/H/N, and M28V + Q30R in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1a replicon, the activity of ombitasvir was reduced by 58- and 243-fold against the M28V and H58D substitutions, respectively, and 800- and 1675-fold by the Q30R and Y93C substitutions, respectively. Y93H, Y93N or M28V in combination with Q30R reduced the activity of ombitasvir by more than 40,000-fold. In genotype 1b, substitutions L31F/V, as well as Y93H alone or in combination with L28M, R30Q, L31F/M/V or P58S in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1b replicon, the activity of ombitasvir was reduced by less than 10-fold by variants at amino acid positions 30 and 31. The activity of ombitasvir was reduced by 77-, 284- and 142-fold against the genotype 1b substitutions Y93H, R30Q in combination with Y93H, and L31M in combination with Y93H, respectively. All other double substitutions of Y93H in combination with substitutions at positions 28, 31, or 58 reduced the activity of ombitasvir by more than 400-fold.

In genotype 1a, substitutions C316Y, M414T, Y448H, A553T, G554S, S556G/R, and Y561H in HCV NS5B reduced susceptibility to dasabuvir. In the genotype 1a replicon, the activity of dasabuvir was reduced 21- to 32-fold by the M414T, S556G or Y561H substitutions; 152- to 261-fold by the A553T, G554S or S556R substitutions; and 1472- and 975-fold by the C316Y and Y448H substitutions, respectively. G558R and D559G/N were observed as treatment-emergent substitutions but the activity of dasabuvir against these variants could not be evaluated due to poor replication capacity. In genotype 1b, substitutions C316N, C316Y,

M414T, Y448H, and S556G in HCV NS5B reduced susceptibility to dasabuvir. The activity of dasabuvir was reduced by 5- and 11-fold by C316N and S556G, respectively; 46-fold by M414T or Y448H; and 1569-fold by the C316Y substitutions in the genotype 1b replicon. Dasabuvir retained full activity against replicons containing substitutions S282T in the nucleoside binding site, M423T in the lower thumb site, and P495A/S, P496S or V499A in the upper thumb site.

Effect of Baseline HCV Substitutions/Polymorphisms on Treatment Response

A pooled analysis of patients in the Phase 2b and 3 clinical trials treated with paritaprevir, ombitasvir, and dasabuvir with or without ribavirin was conducted to explore the association between the baseline NS3/4A, NS5A or NS5B substitutions/polymorphisms and treatment outcome in recommended regimens.

In the greater than 500 genotype 1a baseline samples in this analysis, the most frequently observed resistance-associated variants were M28V (7.4%) in NS5A and S556G (2.9%) in NS5B. Q80K, although a highly prevalent polymorphism in NS3 (41.2% of samples), confers minimal resistance to paritaprevir. Resistance-associated variants at amino acid positions R155 and D168 in NS3 were rarely observed (less than 1%) at baseline. In the greater than 200 genotype 1b baseline samples in this analysis, the most frequently observed resistance-associated variants observed were Y93H (7.5%) in NS5A, and C316N (17.0%) and S556G (15%) in NS5B. Given the low virologic failure rates observed with recommended treatment regimens for HCV genotype 1a- and 1b-infected patients, the presence of baseline variants appears to have little impact on the likelihood of achieving SVR.

Resistance in Clinical Studies

Of the 2,510 HCV genotype 1 infected patients in the Phase 2b and 3 clinical trials treated with regimens containing paritaprevir, ombitasvir, and dasabuvir with or without ribavirin (for 8, 12, or 24 weeks), a total of 74 patients (3%) experienced virologic failure (primarily post-treatment relapse). Treatment-emergent variants and their prevalence in these virologic failure populations are shown in **Table 24**. In the 67 genotype 1a infected patients, NS3 variants were observed in 50 patients, NS5A variants were observed in 46 patients, NS5B variants were observed in 37 patients, and treatment-emergent variants were seen in all 3 drug targets in 30 patients. In the 7 genotype 1b infected patients, treatment-emergent variants were observed in NS3 in 4 patients, in NS5A in 2 patients, and in both NS3 and NS5A in 1 patient. No genotype 1b infected patients had treatment-emergent variants in all 3 drug targets.

Table 24. Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of HOLKIRA PAK with and without Ribavirin Regimens in Phase 2b and Phase 3 Clinical Trials (N = 2510)

Target	Emergent Amino Acid Substitutions[a]	Genotype 1a N = 67[b] % (n)	Genotype 1b N = 7 % (n)
NS3	V55I[c]	6 (4)	-
	Y56H[c]	9 (6)	42.9 (3)[d]
	I132V[c]	6 (4)	-
	R155K	13.4 (9)	-
	D168A	6 (4)	-
	D168V	50.7 (34)	42.9 (3)[d]
	D168Y	7.5 (5)	-
	V36A[c], V36M[c], F43L[c], D168H, E357K[c]	< 5%	-
NS5A	M28T	20.9 (14)	-
	M28V[e]	9 (6)	-
	Q30R[e]	40.3 (27)	-
	Y93H		28.6 (2)
	H58D, H58P, Y93N	< 5%	-
NS5B	A553T	6.1 (4)	-
	S556G	33.3 (22)	-
	C316Y, M414T, G554S, S556R, G558R, D559G, D559N, Y561H	< 5%	-

a. Observed in at least 2 patients of the same subtype.

b. N = 66 for the NS5B target.

c. Substitutions were observed in combination with other emergent substitutions at NS3 position R155 or D168.

d. Observed in combination in genotype 1b-infected patients.

e. Observed in combination in 6% (4/67) of the patients.

Note: The following variants were selected in cell culture but were not treatment-emergent: NS3 variants A156T in genotype 1a, and R155Q and D168H in genotype 1b; NS5A variants Y93C/H in genotype 1a, and L31F/V or Y93H in combination with L28M, L31F/V or P58S in genotype 1b; and NS5B variants Y448H in genotype 1a, and M414T and Y448H in genotype 1b.

Persistence of Resistance-Associated Substitutions

The persistence of paritaprevir, ombitasvir, and dasabuvir resistance-associated amino acid substitutions in NS3, NS5A, and NS5B, respectively, was assessed in genotype 1a-infected patients in Phase 2b trials. Paritaprevir treatment-emergent variants V36A/M, R155K or D168V were observed in NS3 in 47 patients. Ombitasvir treatment-emergent variants M28T, M28V or Q30R in NS5A were observed in 32 patients. Dasabuvir treatment-emergent variants M414T, G554S, S556G, G558R or D559G/N in NS5B were observed in 34 patients.

NS3 variants V36A/M and R155K and NS5B variants M414T and S556G remained detectable at post-treatment Week 48, whereas NS3 variant D168V and all other NS5B variants were not observed at post-treatment Week 48. All treatment-emergent variants in NS5A remained detectable at post-treatment Week 48. Due to high SVR rates in genotype 1b, trends in persistence of treatment-emergent variants in this genotype could not be established.

The lack of detection of virus containing a resistance-associated substitution does not indicate that the resistant virus is no longer present at clinically significant levels. The long-term clinical impact of the emergence or persistence of virus containing HOLKIRA PAK-resistance-associated substitutions is unknown.

Cross-resistance

Cross-resistance is expected among NS5A inhibitors, NS3/4A protease inhibitors, and non-nucleoside NS5B inhibitors by class. The impact of prior ombitasvir, paritaprevir or dasabuvir treatment experience on the efficacy of other NS5A inhibitors, NS3/4A protease inhibitors, or NS5B inhibitors has not been studied.

NON-CLINICAL TOXICOLOGY

General Toxicity

Paritaprevir/ritonavir

Paritaprevir/ritonavir was well tolerated in repeated-dose oral toxicity studies in mice (up to 6-months duration), rats (up to 3-months) and dogs (up to 9-months). The safety margins for studies in the rat, mouse and dog were 15-, 60-, and 210-fold the exposure in human at the recommended dose.

Paritaprevir/ritonavir associated adverse effects were limited to the gallbladder in mice and dogs. In a 6 month mouse study, the adverse findings included focal erosion/ulceration, inflammation (both acute and chronic active), and epithelial hypertrophy/hyperplasia at paritaprevir exposures of 30-fold the exposure in humans at the recommended dose. Gallbladder findings in the dog were limited to minimal epithelial degeneration/necrosis. No evidence of disruption of the epithelial integrity was noted, despite achieving exposures of up to 210-fold the exposure in humans at the recommended dose. The severity and character of the gallbladder change in the dog did not progress from the 1-month to the 9 month toxicology study, despite achieving higher exposures in the 9-month study as compared to the 1-month study.

Ombitasvir

Ombitasvir was well tolerated without adverse effects in repeated-dose oral toxicity studies in mice (up to 6-months duration), rats (up to 3-months) and dogs (up to 6-months). Maximum achieved ombitasvir plasma exposures in the longest duration studies were at least 20-fold or higher as compared to human exposure at the recommended dose.

Both inactive, major, disproportionate human metabolites of ombitasvir (M29, M36) did not cause adverse effects in 1 month repeated-dose studies at AUC exposures that were ≥ 25-fold relative to anticipated human exposures.

Dasabuvir

Dasabuvir was well tolerated in repeated-dose oral toxicity studies in mice (up to 3-months duration), rats (up to 6-months), dogs (up to 9-months) and monkeys (up to 1-month). The safety margins were approximately 30-fold for the rodent (mouse and rat), 120-fold for the dog, and 15-fold for the monkey as compared to human exposure at the recommended dose.

Mutagenicity and Carcinogenicity

Ombitasvir

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in bacterial mutagenicity, human lymphocyte chromosome aberration and *in vivo* mouse micronucleus assays.

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study and a 2-year rat study up to AUC exposures approximately 26- and 16-fold the exposure in humans at the recommended dose.

Paritaprevir/ritonavir

Paritaprevir was positive for genotoxicity in an *in vitro* human chromosome aberration test but negative in a bacterial mutation assay, and in two *in vivo* genetic toxicology assays (rat bone marrow micronucleus and rat liver Comet tests).

Ritonavir was not genotoxic in bacterial mutation assay, mouse lymphoma assay, chromosomal aberration assay and in vivo mouse micronucleus test.

Paritaprevir/ritonavir was not carcinogenic in a 6-month transgenic mouse study up to AUC exposures approximately 38- and 4-fold the exposure in humans at the recommended dose. Similarly, paritaprevir/ritonavir was not carcinogenic in a 2-year rat study up to AUC exposures approximately 8- and 4-fold the exposure in humans at the recommended dose.

Dasabuvir

Dasabuvir was not genotoxic in bacterial mutagenicity, human lymphocyte chromosome aberration and *in vivo* rat micronucleus assays.

Dasabuvir was not carcinogenic in a 6-month transgenic mouse study and a 2-year rat study up to AUC exposures approximately 19-fold the exposure in humans at the recommended dose.

Use with Ribavirin

Ribavirin was shown to be genotoxic in several *in vitro* and *in vivo* assays. Ribavirin was not carcinogenic in a 6-month p53+/- transgenic mouse study or a 2-year rat study. See the Product Monograph for ribavirin for additional information.

Fertility

Ombitasvir

Ombitasvir had no effects on fertility when evaluated in mice up to AUC exposures approximately 25-fold the exposure in humans at the recommended clinical dose.

Paritaprevir/ritonavir

Paritaprevir/ritonavir had no effects on fertility when evaluated in rats up to AUC exposures approximately 8- and 2-fold higher than the exposure in humans at the recommended clinical dose.

Dasabuvir

Dasabuvir had no effects on fertility when evaluated in rats up to AUC exposures approximately 16-fold the exposure in humans at the recommended clinical dose.

Use with Ribavirin

In fertility studies in male animals, ribavirin induced reversible testicular toxicity. Refer to Product Monograph for ribavirin for additional information.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrHOLKIRA® PAK

ombitasvir/paritaprevir/ritonavir film-coated tablets and dasabuvir film-coated tablets

Read this carefully before you start taking HOLKIRA PAK and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your doctor about your medical condition and treatment and ask if there is any new information about HOLKIRA PAK.

Serious Warnings and Precautions

Hepatitis B activity (e.g., inflamed liver) may increase when taking antiviral drugs like HOLKIRA PAK, sometimes leading to liver failure and death. (See the "To help avoid side effects…" section, *Hepatitis B Reactivation*)

What is HOLKIRA PAK used for?

HOLKIRA PAK treats long-lasting hepatitis C virus (HCV) infection in adults 18 years and older. It treats one kind of HCV infection called HCV genotype 1.

HOLKIRA PAK is sometimes used with ribavirin, but not always. Read the ribavirin patient medication information if your doctor says you should also take ribavirin.

How does HOLKIRA PAK work?

HOLKIRA PAK with ribavirin can cure HCV infection in most patients. Cure means HCV is cleared from your blood 3 months after finishing the medicine.

HOLKIRA PAK has 3 types of HCV medicines. These 3 medicines stop HCV from multiplying in different ways.

Curing HCV infection can help lower the chance you will have problems or die from HCV.

Taking HOLKIRA PAK does not keep you from getting infected again. Talk with your doctor about ways to avoid getting infected again with HCV.

Can I still pass on HCV to others if I take HOLKIRA PAK?

Yes, you can still pass on HCV to others while you are taking HOLKIRA PAK. For example, some ways that HCV can be passed on is by sharing needles or through unprotected sex. Talk with your doctor about ways to avoid passing on HCV.

What are the ingredients in HOLKIRA PAK?

Ombitasvir/paritaprevir/ritonavir tablets

Each tablet contains the following medicinal ingredients: ombitasvir, paritaprevir and ritonavir.

Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, propylene glycol monolaurate, sodium stearyl fumarate, sorbitan monolaurate, vitamin E polyethylene glycol succinate.

Each tablet is covered with the following ingredients that are not medicines: iron oxide red, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide.

The tablets do not contain gluten.

Dasabuvir film-coated tablets

Each tablet contains the following medicinal ingredients: dasabuvir.

Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Each tablet is covered with the following ingredients that are not medicines: iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide.

The tablets do not contain gluten.

HOLKIRA PAK comes in the following dosage forms:

HOLKIRA PAK has two different tablets. One tablet has 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir. The other tablet has 250 mg of dasabuvir.

Do not use HOLKIRA PAK if:

- your doctor says you should also use ribavirin and you are pregnant or want to be pregnant (or your partner is pregnant or wants to become pregnant). Ribavirin may cause birth defects or death of your unborn baby.
- you are allergic to any of the medicines or other ingredients in HOLKIRA PAK (see the

section **What are the ingredients in HOLKIRA PAK?** to see all the medicines and ingredients).

- your doctor has told you that you have moderate or severe loss of liver function.
- you are taking any of the following medicines or natural substances:
  - alfuzosin hydrochloride (Xatral®)
  - astemizole*
  - bosentan (Tracleer®)
  - carbamazepine (Tegretol®)
  - cisapride*
  - colchicine for patients who have certain kidney or liver problems
  - dronedarone (Multaq®)
  - efavirenz-containing medicines (Sustiva®, Atripla®)
  - ergot-containing medicines including:
    - ergonovine*
    - ergotamine tartrate*
    - ergotamine (Bellergal Spacetabs®)
    - dihydroergotamine mesylate (Migranal®)
    - methylergonovine*
  - ethinyl estradiol-containing medicines such as those contained in most contraceptive pills and vaginal rings used for contraception
  - etravirine (Intelence®)
  - fusidic acid (systemic)*
  - gemfibrozil
  - lovastatin
  - lurasidone (Latuda®)
  - midazolam (when taken by mouth)
  - modafinil (Alertec®)
  - nevirapine (Viramune®)
  - phenytoin (Dilantin®)
  - phenobarbital
  - pimozide (Orap®)
  - rifampin (Rifadin®, Rifater®, Rofact®)
  - salmeterol (Advair Diskus®, Serevent Diskus®)
  - sildenafil citrate (Revatio®) for the lung problem, pulmonary artery hypertension (PAH)
  - simvastatin
  - St. John's wort (*Hypericum perforatum*) or products containing St. John's wort
  - terfenadine*
  - triazolam

*** Drugs not sold in Canada.**

To help avoid side effects and make sure you are using your medicines correctly, talk to your doctor before you take HOLKIRA PAK. Talk about any health problems you may have, including if you:

- are taking birth control medicines of any kind or using a medicine that has ethinyl estradiol. Ethinyl estradiol is usually found in birth control pills. However, not all birth control pills have ethinyl estradiol. You must not use medicines that have ethinyl estradiol while taking HOLKIRA PAK. Your doctor will ask you to stop or change to a different type of birth control while you are taking HOLKIRA PAK.
- have any other medical condition.
- have had a kidney and/or liver transplant.
    - You should not take HOLKIRA PAK if you are taking everolimus. The dose of everolimus cannot be adjusted to maintain the correct drug levels when given with HOLKIRA PAK.
    - If you are taking tacrolimus, you should talk to your doctor about the risks and benefits of taking HOLKIRA PAK at the same time and consider:
        - Serious and life-threatening side effects have occurred when taking HOLKIRA PAK with tacrolimus
        - Your doctor may order blood tests to check tacrolimus levels in your blood at the beginning and during treatment with HOLKIRA PAK
    - Talk with your doctor if you are taking cyclosporine for your transplant. The levels of this medicine can change when taken with HOLKIRA PAK. Your doctor will choose how much cyclosporine you need to take:
        - with HOLKIRA PAK.
        - when you have completed HOLKIRA PAK.
        - if you have to stop taking HOLKIRA PAK for any reason.
- have liver problems other than HCV infection.
- also have HIV infection.
- are breastfeeding or plan to breastfeed. It is not known if HOLKIRA PAK passes into your breast milk. You and your doctor should decide if you will take HOLKIRA PAK or breastfeed. You should not do both.

Hepatitis B Reactivation

Taking antiviral drugs such as HOLKIRA PAK may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Contact your doctor if:

- you have never been tested for hepatitis B
- you know you have a current hepatitis B infection
- you have had a previous hepatitis B infection

Your healthcare professional may do blood tests:

- before hepatitis C treatment
- to see the hepatitis B levels in your blood
- and may order hepatitis B treatment

Pregnancy and Birth Control

- Females must have negative pregnancy test before starting HOLKIRA PAK and ribavirin, every month while on the medicine, and for 6 months after stopping them.
- You or your partner should not become pregnant while taking HOLKIRA PAK with ribavirin and for 6 months after you have stopped taking them.
- You and your partner must use 2 kinds of birth control while taking HOLKIRA PAK and ribavirin and for 6 months after you have stopped taking them.
- Talk with your doctor about the kind of birth control that you can use.
- If you or your partner becomes pregnant while taking HOLKIRA PAK and ribavirin or within 6 months after you stop taking them, tell your doctor right away.

Other warnings you should know about:

HOLKIRA PAK may cause severe liver problems, especially in people with advanced cirrhosis (liver scarring). These severe liver problems can lead to the need for a liver transplant, or can lead to death.

Rises in liver tests have occurred when the medicines that are in HOLKIRA PAK were taken in studies. Contact your doctor right away if you have symptoms like those listed below since these may mean you have a serious problem with your liver:

- loss of appetite (do not feel like eating)
- stomachache

- swelling of your stomach area
- nausea (feeling sick in the stomach)
- vomiting
- feeling tired or weak
- yellowing of the skin and eyes
- confusion
- dark urine and pale stool.

It is not known if taking HOLKIRA PAK is safe or will work in children under 18 years of age.

Your doctor may do blood tests before you start taking, and while you are on your medicines. This is to help check if the medicines are working for you.

Tell your doctor all the medicines, drugs, vitamins and minerals, natural supplements or alternative medicines you are already taking. Also tell your doctor if you stop any of these or start any new ones.

Do not take HOLKIRA PAK with the following medicines:

- other ritonavir-containing medicines (Norvir®, Kaletra®). When given with HOLKIRA PAK, atazanavir and darunavir should be taken without ritonavir.
- amiodarone (Cordarone®)
- alfentanil
- disopyramide (Rythmodan®)
- everolimus (Affinitor®, Affinitor® Disperz)
- fentanyl (Abstral®, Duragesic®)
- flecainamide
- lidocaine (systemic)
- propafenone (Rythmol®)
- quetiapine (Seroquel®)
- quinidine
- rilpivirine (Edurant®, Complera®)
- sirolimus (Rapamune®)

The following medicines may interact with HOLKIRA PAK:

- alprazolam (Xanax®)
- amlodipine (Norvasc®)
- atazanavir (Reyataz®)
- atorvastatin (Lipitor®)
- carisoprodol*

- candesartan (Atacand®/Atacand® Plus)
- cyclobenzaprine
- cyclosporine (Neoral®, Sandimmune®)
- darunavir (Prezista®)
- diazepam (Valium®)
- digoxin (Lanoxin®)
- diltiazem (Cardizem® CD)
- fluticasone (Advair®, Flonase®, Flovent Diskus®, Flovent HFA®)
- fluvastatin (Lescol®)
- furosemide (Lasix®)
- hydrocodone (Hycodan®, Novahistex®, Novahistine ®, Tussionex®)
- itraconazole (Sporanox®)
- ketoconazole (Nizoral®)
- losartan (Cozaar®/Hyzaar®)
- nifedipine (Adalat® XL)
- omeprazole (Losec®)
- pitavastatin*
- posaconazole (Posanol®)
- pravastatin (Pravachol®)
- rosuvastatin (Crestor®)
- tacrolimus (Prograf®)
- valsartan (Diovan®/ Diovan® HCT)
- verapamil (Isoptin® SR)
- voriconazole (Vfend®)
- warfarin (Coumadin®)

*** Drugs not sold in Canada.**

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Keep a list of all the medicines you take. Show it to your doctor or pharmacist when you get a new medicine or stop a medicine.

If you change or stop one of your other medicines while you are taking HOLKIRA PAK, ask your doctor about changing back when you are finished taking HOLKIRA PAK.

How to take HOLKIRA PAK:

- Take HOLKIRA PAK exactly as your doctor tells you. Do not change your dose or stop unless your doctor tells you to.
- Take HOLKIRA PAK at about the same time every day with food. The type of food is not important.
- Swallow HOLKIRA PAK tablets whole with water or another liquid if needed.

- Do not chew, break, or crush HOLKIRA PAK tablets.

Usual Adult Dose:

- Every day in the morning, take the two pink ombitasvir/paritaprevir/ritonavir tablets and one beige dasabuvir tablet with food.
- Every day in the evening, take the remaining beige dasabuvir tablet with food.
- HOLKIRA PAK is taken for either 12 or 24 weeks. Your doctor will tell you exactly how long you need to take HOLKIRA PAK.
- If your doctor has also prescribed ribavirin, your doctor will provide you dosage directions for the ribavirin.

Overdose:

If you think you have taken too much HOLKIRA PAK, contact your doctor or pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if you do not have symptoms.

Missed Dose:

- If you miss a dose of the pink ombitasvir/paritaprevir/ritonavir tablets and it is:
    - less than 12 hours from the time you usually take ombitasvir/paritaprevir/ritonavir, you should take the missed dose with food as soon as possible. Then take your next dose at your usual time.
    - more than 12 hours from the time you usually take ombitasvir/paritaprevir/ritonavir, you should not take the missed dose. Take your next dose as usual with food.
- If you miss a dose of the beige dasabuvir tablets and it is:
    - less than 6 hours from the time you usually take dasabuvir, you should take the missed dose with food as soon as possible. Then take your next dose at your usual time.
    - more than 6 hours from the time you usually take dasabuvir, you should not take the missed dose. Take your next dose as usual with food.

What are possible side effects from using HOLKIRA PAK?

If your side effect is not listed here, contact your doctor or pharmacist. Also see **Other warnings you should know about.**

Common side effects of HOLKIRA PAK:

- feeling tired or weak
- headache

Common side effects of HOLKIRA PAK when used with ribavirin:

- feeling tired or weak
- headache
- itching
- nausea (feeling sick in the stomach)
- trouble sleeping

Hypersensitivity (allergic reactions) with symptoms such as swollen lips and tongue have been reported for HOLKIRA PAK.

If you have a side effect that is not listed here or becomes bad enough to get in the way of your daily tasks, talk to your doctor.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

NOTE: Contact your doctor if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2 and 30°C. Keep away from moisture.

Keep HOLKIRA PAK out of the reach and sight of children.

If you want more information about HOLKIRA PAK:

- Talk to your doctor.
- Find the most recent version of the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website (abbvie.ca), or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

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Abstral, Adalat XL, Advair, Advair Diskus, Affinitor, Affinitor Disperz, Alertec, Atacand, Atacand Plus, Atripla, Bellergal Spacetabs, Cardizem CD, Complera, Cordarone, Coumadin, Cozaar, Crestor, Dilantin, Diovan, Diovan HCT, Duragesic, Edurant, Flonase, Flovent Diskus, Flovent HFA, Hycodan,Hyzaar, Intelence, Isoptin SR, Lanoxin, Lasix, Latuda, Lescol, Lipitor, Losec, Migranal, Multaq, Neoral, Nizoral, Norvasc, Novahistex, Novahistine ,Orap, Posanol, Pravachol, Prezista, Prograf, Rapamune, Revatio, Reyataz, Rifadin, Rifater, Rofact, Rythmodan, Rythmol, Sandimmune, Serevent Diskus, Seroquel, Sporanox, Sustiva, Tegretol, Tracleer, Tussionex, Valium, Vfend, Viramune, Xanax, Xatral are trademarks of their respective owners and are not trademarks of AbbVie Corporation. The makers of these brands are not affiliated with and do not endorse AbbVie or its products.

THE ATTACHED IS EXHIBIT "G" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 13TH DAY OF OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ZEPATIER™

elbasvir/grazoprevir tablets

50 mg/100 mg

Antiviral Agent

Merck Canada Inc.
16750 route Transcanadienne
Kirkland QC Canada H9H 4M7
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Date of Preparation:
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ZEPATIER™

50 mg of elbasvir and 100 mg of grazoprevir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablet 50 mg elbasvir and 100 mg grazoprevir	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ZEPATIER™ (elbasvir/grazoprevir) is indicated for the treatment of chronic hepatitis C (CHC) genotypes 1, 3, or 4 infection in adults as follows:

Without ribavirin:
- in genotype (GT) 1 or 4 treatment-naïve (TN) and peginterferon alfa + ribavirin (PR) treatment-experienced (TE) relapsers (12 weeks)
- in GT1 protease inhibitor (PI)/PR-TE relapsers (12 weeks)
- in GT1b TN, non-cirrhotic patients (8 weeks)
- in GT1b PR- or PI/PR-TE on-treatment virologic failures (12 weeks)

With ribavirin:
- in GT1a PR- or PI/PR-TE on-treatment virologic failures (16 weeks)
- in GT4 PR-TE on-treatment virologic failures (16 weeks)

With sofosbuvir:
- in GT3 TN patients (12 weeks)

(see **DOSAGE AND ADMINISTRATION**)

Geriatrics (> 65 years of age):
There were a limited number of geriatrics patients (N=187) included in the clinical trials. There was no overall difference in safety or efficacy observed in these patients (**see WARNINGS AND PRECAUTIONS, Special Populations**).

Pediatrics (< 18 years of age):
Safety and efficacy of ZEPATIER™ have not been established in pediatric patients less than 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- If ZEPATIER™ is administered with ribavirin or sofosbuvir, the contraindications to ribavirin or sofosbuvir also apply to this combination regimen. Refer to the ribavirin or sofosbuvir product monograph for a list of contraindications for ribavirin or sofosbuvir.
- ZEPATIER™ is contraindicated in patients with moderate or severe hepatic impairment (see **WARNINGS AND PRECAUTIONS, Special Populations, ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY**).
- ZEPATIER™ is contraindicated with organic anion transporting polypeptide 1B (OATP1B) inhibitors, strong inducers of cytochrome P450 3A (CYP3A), or efavirenz.

Table 1 - Drugs that are Contraindicated with ZEPATIER™

Mechanism of Interaction	Clinical Comment	Drugs that are Contraindicated with ZEPATIER™*
Inhibition of OATP1B by co-administred drug	May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations	Antimycobacterials rifampin HIV medications atazanavir darunavir lopinavir saquinavir tipranavir Immunosuppressants cyclosporine
Strong induction of CYP3A by co-administered drugs	May lead to loss of virologic response to ZEPATIER™ due to significant decreases in elbasvir and grazoprevir plasma concentrations	Anticonvulsants phenytoin, carbamazepine Herbal products St. John's Wort (Hypericum perforatum) HIV medications efavirenz†

* This table is not a comprehensive list of all drugs that inhibit OATP1B.
† Efavirenz is included as a strong CYP3A inducer in this table, since co-administration reduced grazoprevir exposure by ≥ 80% (see Table 10)

WARNINGS AND PRECAUTIONS

General
Since ZEPATIER™ is a fixed dose combination product, an adjustment of its recommended dose is not possible.

Risks Associated with Ribavirin Combination
If ZEPATIER™ is administered with ribavirin, the warnings and precautions for ribavirin, including the pregnancy avoidance warning, also apply to this combination regimen. Refer to the ribavirin product monograph for a list of warnings and precautions for ribavirin.

Risks Associated with Sofosbuvir Combination
If ZEPATIER™ is administered with sofosbuvir, the warnings and precautions for sofosbuvir, also apply to this combination regimen. Refer to the sofosbuvir prescribing information for a list of warnings and precautions for sofosbuvir.

Drug Interactions
Co-administration of ZEPATIER™ and OATP1B inhibitors may significantly increase grazoprevir plasma concentrations and is contraindicated (see **DRUG INTERACTIONS**).

The concomitant use of ZEPATIER™ and strong CYP3A inducers or efavirenz may significantly decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced therapeutic effect of ZEPATIER™. Therefore, the use of ZEPATIER™ with strong CYP3A inducers or efavirenz is contraindicated (see **DRUG INTERACTIONS**).

The concomitant use of ZEPATIER™ and moderate CYP3A inducers may decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced therapeutic effect of ZEPATIER™. Therefore, the use of ZEPATIER™ with moderate CYP3A inducers is not recommended.

The concomitant use of ZEPATIER™ and strong CYP3A inhibitors increases elbasvir and grazoprevir concentrations. Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended.

The plasma concentration of grazoprevir is increased if ZEPATIER™ is co-administered with cyclosporine. Co-administration with cyclosporine is contraindicated (see **DRUG INTERACTIONS**).

See Table 8 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during ZEPATIER™ therapy; review concomitant medications during ZEPATIER™ therapy; and monitor for the adverse reactions associated with the concomitant drugs (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Hepatic

Increased Risk of ALT Elevations

During clinical trials with ZEPATIER™ with or without ribavirin, < 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in females (2% [11/652]), Asians (2% [4/165]), and subjects aged ≥65 years (2% [3/187]). (see **ADVERSE REACTIONS**).

Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12.

- Patients should be instructed to consult their healthcare professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces.
- ZEPATIER™ should be discontinued if ALT levels remain persistently greater than 10 times the ULN or accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ration (INR).

Hepatic Impairment

ZEPATIER™ may be used as recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER™ is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B and Child-Pugh C, respectively) due to a lack of clinical safety and efficacy experience in these patient populations, the expected increase in grazoprevir exposure (approximately 5-or 12-fold, respectively), and the increased risk of late ALT elevations. (see **CONTRAINDICATIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Liver Transplant Patients

The safety and efficacy of ZEPATIER™ have not been established in patients awaiting liver transplant or in liver transplant recipients.

Special Populations

Pregnant Women

Pregnancy should be avoided while taking ZEPATIER™ as there are no data on the use of ZEPATIER™ in pregnant women. Patients should be advised to notify their health care provider immediately in the event of a pregnancy. ZEPATIER™ should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Elbasvir: No effects on embryo-fetal development or maternal toxicity have been observed in rats or rabbits when dams were administered elbasvir up to the highest dose tested (approximately 9 and 17 times the clinical dose based on AUC, respectively). In both species, elbasvir was shown to cross the placenta. In the pre- and postnatal study, no effects have been observed in rat offspring when exposed in utero (via maternal dosing) and during lactation (via

maternal milk) up to the highest maternal exposure tested (approximately 9 times the clinical dose based on AUC).

Grazoprevir: No effects on embryo-fetal development or maternal toxicity have been observed in rats or rabbits when dams were administered grazoprevir up to the highest dose tested (approximately 110 and 39 times the clinical dose based on AUC, respectively). In both species, grazoprevir was shown to cross the placenta. In the pre- and postnatal study, no effects have been observed in rat offspring when exposed in utero (via maternal dosing) and during lactation (via maternal milk) up to the highest maternal exposure tested (approximately 79 times the clinical dose based on AUC).

Nursing Women
There are no human data to assess whether ZEPATIER™ is excreted in human breast milk. A risk to the newborn/infant cannot be excluded, therefore mothers should be instructed not to breastfeed if they are taking ZEPATIER™. Elbasvir and grazoprevir are excreted in the milk of lactating rats. Concentrations of elbasvir were higher and concentrations of grazoprevir were lower in breast milk than maternal plasma in rats.

Females and Males of Reproductive Potential
No human data on the effect of elbasvir and grazoprevir on fertility are available. In rats, elbasvir and grazoprevir had no effect on fertility when tested at approximately 9 and 117 and times the clinical dose based on AUC, respectively.

Pediatrics (< 18 years of age)
Safety and efficacy of ZEPATIER™ have not been established in pediatric patients less than 18 years of age.

Geriatrics (> 65 years of age)
Clinical trials of ZEPATIER™ with or without ribavirin included 187 subjects aged 65 and over. Although higher elbasvir and grazoprevir plasma concentrations were observed in subjects aged 65 and over, no overall differences in safety or efficacy were observed between subjects aged 65 and over and younger (see **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Impairment
In patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or with end stage renal disease (ESRD), including patients on hemodialysis, it is recommended to administer ZEPATIER™ without ribavirin (see **DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY**).

Other Hepatitis C Virus (HCV) Genotypes
Safety and efficacy of ZEPATIER™ have not been established in patients infected with HCV genotypes 2, 5, and 6. (see **INDICATIONS AND CLINICAL USE**)

HCV/HIV-1 co-infection
Co-administration of ZEPATIER™ and OATP1B inhibitors (including HIV protease inhibitors), is contraindicated. The use of ZEPATIER™ with strong CYP3A inducers or efavirenz is

contraindicated. The use of ZEPATIER™ with moderate CYP3A inducers and the fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate is not recommended (see **DRUG INTERACTIONS**).

HCV/HBV (Hepatitis B Virus) co-infection
The safety and efficacy of ZEPATIER™ have not been studied in HCV/HBV co-infected patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
If ZEPATIER™ is administered with ribavirin or sofosbuvir, refer to the product monographs for ribavirin or sofosbuvir for a list of ribavirin or sofosbuvir-associated adverse reactions.

The safety summary of ZEPATIER™ was based on data from two placebo-controlled trials and eight uncontrolled Phase 2 and 3 clinical trials in approximately 2,000 subjects with chronic hepatitis C infection with compensated liver disease (with or without cirrhosis) who received ZEPATIER™ with or without ribavirin (see **CLINICAL TRIALS**).

Adverse Reactions in Subjects Receiving ZEPATIER™ Alone
C-EDGE TN was a Phase 3 placebo-controlled trial in treatment-naïve (TN) subjects. The most commonly reported adverse reactions (adverse events assessed as causally related by the investigator, all grades) occurring in C-EDGE TN at ≥ 10% frequency in subjects treated with ZEPATIER™ for 12 weeks were fatigue and headache. No subjects had serious adverse reactions. The proportion of subjects who permanently discontinued treatment due to adverse reactions was < 1%.

In a pooled analysis of Phase 2 and 3 clinical trials in subjects treated with ZEPATIER™ for 12 weeks, the most commonly reported adverse reactions (greater than 10% of subjects) were fatigue and headache. The majority of the adverse reactions were mild in severity. No subjects treated with ZEPATIER™ had serious adverse reactions. The proportion of subjects who permanently discontinued treatment due to adverse reactions was < 1%. The type and severity of adverse reactions in subjects with cirrhosis were comparable to those seen in subjects without cirrhosis.

Adverse Reactions in Subjects Receiving ZEPATIER™ with Ribavirin
C-EDGE TE was a Phase 3 open-label trial in treatment-experienced (TE) subjects. The most commonly reported adverse reactions occurring in C-EDGE TE at ≥ 10% frequency in subjects treated with ZEPATIER™ with ribavirin for 16 weeks were fatigue, headache, anemia and nausea. The majority of the adverse reactions were mild in severity. The proportion of subjects treated with ZEPATIER™ with ribavirin with serious adverse reactions was < 1%. The portion of subjects who permanently discontinued treatment due to adverse reactions was 2%. The type and severity of adverse reactions in subjects with cirrhosis were comparable to those seen in subjects without cirrhosis.

ZEPATIER™ in Subjects with Advanced Chronic Kidney Disease

The safety of elbasvir and grazoprevir in comparison to placebo in subjects with advanced chronic kidney disease (severe renal impairment or ESRD, including patients on hemodialysis) and genotype 1 CHC infection with compensated liver disease (with or without cirrhosis) was assessed in 235 subjects (C-SURFER) (see **CLINICAL TRIALS**). The most commonly reported adverse reactions occurring at ≥ 10% frequency in subjects treated with ZEPATIER™ were nausea and headache. The majority of the adverse reactions were mild in severity. No subjects experienced a serious adverse reaction or discontinued treatment due to adverse reactions.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Reactions in Subjects Receiving ZEPATIER™ Alone

Adverse reactions (adverse events assessed as causally related by the investigator, all grades) occurring at ≥ 5% frequency in subjects treated with ZEPATIER™ for 12 weeks in C-EDGE TN or with ZEPATIER™ for 12 weeks in the pooled analysis of Phase 2 and 3 clinical trials are presented in Table 2.

Table 2 - Adverse Reactions Occurring at ≥ 5% Frequency in Subjects with Chronic Hepatitis C Infection Treated with ZEPATIER™ for 12 Weeks in C-EDGE TN or with ZEPATIER™ for 12 weeks in the Pooled Phase 2 and 3 Clinical Trials

	C-EDGE TN		Pooled[†]
	ZEPATIER™ N=316 % (n) 12 weeks	**Placebo N=105 % (n) 12 weeks**	**ZEPATIER™ N=834 % (n) 12 weeks**
Fatigue	11% (35)	10% (10)	11% (94)
Headache	10% (31)	9% (9)	10% (86)
Nausea	4% (14)	5% (5)	5% (43)
[†]Includes C-WORTHY, C-SCAPE, C-SALT, C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE and P058			

The type and severity of adverse reactions were comparable among subjects treated with 8, 12 or 16 weeks of ZEPATIER™.

Common Clinical Trial Adverse Drug Reactions (≥ 1% to < 5%)

Adverse reactions occurring in a pooled analysis of Phase 2 and 3 clinical trials at ≥1% to < 5% frequency in subjects treated with ZEPATIER™ for 12 weeks are listed below by body system (Table 3).

Table 3 - Adverse Reactions Occurring at ≥ 1% to <5% Frequency in Subjects with Chronic Hepatitis C Infection Treated with ZEPATIER™ for 12 weeks in the Pooled Phase 2 and 3 Clinical Trials

Body System	**Adverse Drug Reactions (%)**
Gastrointestinal disorders:	Abdominal pain (2%), abdominal pain upper (2%), constipation (2%), diarrhea (3%), dry mouth (1%), vomiting (1%)
General disorders and administration site conditions:	Asthenia (4%)
Metabolism and nutrition disorders:	Decreased appetite (2%)
Musculoskeletal and connective tissue disorders:	Arthralgia (2%), myalgia (2%)
Nervous system disorders:	Dizziness (2%)
Psychiatric disorders:	Anxiety (1%), depression (1%), insomnia (3%), irritability (2%)
Skin and subcutaneous tissue disorders:	Alopecia (1%)
Skin and subcutaneous tissue disorders:	Pruritus (1%)

Adverse Reactions in Subjects Receiving ZEPATIER™ with Ribavirin

Adverse reactions occurring in C-EDGE TE at ≥ 5% frequency in subjects treated with ZEPATIER™ with ribavirin for 16 weeks are presented in Table 4.

Table 4 - Adverse Reactions Occurring at ≥ 5% Frequency in Subjects with Chronic Hepatitis C Infection Treated with ZEPATIER™ + Ribavirin for 16 Weeks in C-EDGE TE

	C-EDGE TE
	ZEPATIER™ + Ribavirin N=106 % (n) 16 weeks
Fatigue	25% (27)
Headache	17% (18)
Anemia	16% (17)
Nausea	12% (13)
Pruritus	9% (10)
Asthenia	8% (9)
Dyspepsia	6% (6)
Dyspnea	8% (9)
Hemoglobin decreased	7% (7)
Dyspnea exertional	6% (6)
Insomnia	6% (6)
Myalgia	6% (6)
Vomiting	6% (6)
Decreased appetite	5% (5)
Cough	5% (5)
Irritability	5% (5)
Rash	5% (5)

Common Clinical Trial Adverse Drug Reactions (≥ 1% to < 5%)

Adverse reactions occurring in C-EDGE TE at ≥1% to < 5% frequency in subjects treated with ZEPATIER™ with ribavirin for 16 weeks are listed below by body system (Table 5).

Table 5 - Adverse Reactions Occurring at ≥1 to < 5% Frequency in Subjects with Chronic Hepatitis C Infection Treated with ZEPATIER™ + Ribavirin for 16 Weeks in C-EDGE TE

Body System	Adverse Drug Reactions (%)
Blood and lymphatic system disorders:	Haemolytic anemia (2%)
Cardiac disorders:	Palpitations (2%)
Eye disorders:	Ocular icterus (2%)
Gastrointestinal disorders:	Abdominal pain (2%), constipation (3%), diarrhea (4%), flatulence (2%)
Hepatobiliary disorders:	Hyperbilirubinaemia (2%)
Investigations:	Haematocrit decreased (2%)
Musculoskeletal and connective tissue disorders:	Arthralgia (2%)
Nervous system disorders:	Dizziness (3%), dysgeusia (3%), lethargy (2%), memory impairment (2%), presyncope (2%)
Psychiatric disorders:	Anxiety (2%), depression (3%), sleep disorder (3%)
Skin and subcutaneous tissue disorders:	Alopecia (3%), dry skin (4%), pruritus generalized (2%), rash maculo-papular (2%)

Abnormal Hematologic and Clinical Chemistry Findings in Subjects Receiving ZEPATIER™ with or without Ribavirin

Serum ALT Elevations

During clinical trials with ZEPATIER™ with or without ribavirin, regardless of treatment duration, < 1% (13/1690) of subjects experienced elevations of ALT from normal levels to greater than 5 times the ULN, generally at or after treatment week 8 (mean onset time 10 weeks, range 6-12 weeks). Most ALT elevations resolved with ongoing therapy with ZEPATIER™ or after completion of therapy. The frequency of ALT elevations was higher in subjects with higher grazoprevir plasma concentration. The incidence of late ALT elevations was not affected by treatment duration. Cirrhosis was not a risk factor for ALT elevations. (see **WARNINGS AND PRECAUTIONS, Hepatic, DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**)

Serum Bilirubin Elevations

During clinical trials with ZEPATIER™ with or without ribavirin, regardless of treatment duration, elevations in bilirubin at greater than 2.5 times ULN were observed in 6% of subjects receiving ZEPATIER™ with ribavirin compared to < 1% in those receiving ZEPATIER™ alone. These bilirubin increases were predominantly indirect bilirubin and were generally observed in association with ribavirin co-administration. Bilirubin elevations were typically not associated with serum ALT elevations.

Decreased Hemoglobin

During clinical trials with ZEPATIER™ with or without ribavirin, the mean change from baseline in hemoglobin levels in subjects treated with ZEPATIER™ for 12 weeks was -0.19 mmol/L (–0.3 g/dL) and with ZEPATIER™ with ribavirin for 16 weeks was approximately -1.37 mmol/L (–2.2 g/dL). Hemoglobin declined during the first 8 weeks of treatment, remained low during the remainder of treatment, and normalized to baseline levels during follow-up. Less than 1% of subjects treated with ZEPATIER™ with ribavirin had hemoglobin levels decrease to less than 5.28 mmol/L (8.5 g/dL) during treatment. No subjects treated with ZEPATIER™ alone had a hemoglobin level less than 5.28 mmol/L (8.5 g/dL).

ZEPATIER™ in Subjects with HCV/HIV-1 Co-Infection

The type and severity of adverse reactions in subjects with HCV/HIV-1 co-infection (n=298) were comparable to subjects without HCV/HIV-1 co-infection.

ZEPATIER™ in Subjects with Advanced Chronic Kidney Disease

The adverse reactions occurring in C-SURFER at ≥ 5% frequency in subjects treated with ZEPATIER™ for 12 weeks are presented in Table 6.

Table 6 - Adverse Reactions Occurring at ≥ 5% Frequency in Subjects with Advanced Chronic Kidney Disease and Chronic Hepatitis C Infection Treated with ZEPATIER™ in C-SURFER

	ZEPATIER™ N=122 % (n) 12 weeks	**Placebo N=113 % (n) 12 weeks**
Nausea	11% (14)	8% (9)
Headache	11% (14)	5% (6)
Fatigue	5% (6)	8% (9)

Common Clinical Trial Adverse Drug Reactions (≥ 1% to < 5%)

Adverse reactions occurring in C-SURFER at ≥1% to < 5% frequency in subjects during treatment with ZEPATIER™ for 12 weeks are listed below by body system (Table 7).

Table 7 - Adverse Reactions Occurring at ≥ 1% to <5% Frequency in Subjects with Advanced Chronic Kidney Disease and Chronic Hepatitis C Infection Treated with ZEPATIER™ in C-SURFER

Body System	**Adverse Drug Reactions (%)**
Ear and labyrinth disorders	Tinnitus (2%)
Gastrointestinal disorders:	Diarrhoea (2%), dry mouth (2%), dyspepsia (2%), flatulence (2%), vomiting (2%)
General disorders and administration site conditions:	Asthenia (4%)
Investigations:	Blood creatine phosphokinase increased (2%)
Metabolism and nutrition disorders:	Decreased appetite (2%)
Nervous system disorders:	Dizziness (3%)
Psychiatric disorders:	Insomnia (4%)
Skin and subcutaneous tissue disorders	Night sweats (2%), pruritus (2%)

Adverse Reactions in Subjects Receiving ZEPATIER™ with Sofosbuvir

The safety of ZEPATIER™ with sofosbuvir in treatment-naïve subjects with chronic hepatitis C genotype 3 infection was assessed in 143 subjects (C-SWIFT safety population). No adverse reactions were reported at ≥ 5% frequency. The adverse reactions occurring at ≥1% to <5% frequency were diarrhea (1%), fatigue (1%), nausea (2%) and headache (3%). No subjects treated with ZEPATIER™ had serious adverse reactions and no subjects permanently discontinued treatment due to adverse reactions) (see **CLINICAL TRIALS**).

DRUG INTERACTIONS

Overview
(See also **WARNINGS AND PRECAUTIONS**)

As ZEPATIER™ contains elbasvir and grazoprevir, interactions that have been identified with these agents individually may occur with ZEPATIER™.

Effects of Other Drugs on ZEPATIER™
Elbasvir and grazoprevir are substrates of CYP3A and P-gp. Co-administration of strong inducers of CYP3A or efavirenz with ZEPATIER™ may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER™. Co-administration of ZEPATIER™ with strong CYP3A inducers or efavirenz is contraindicated (see **CONTRAINDICATIONS).** Co-administration of moderate inducers of CYP3A with ZEPATIER™ may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER™. Co-administration of ZEPATIER™ with moderate CYP3A inducers is not recommended (see **WARNINGS AND PRECAUTIONS**). Co-administration of ZEPATIER™ with strong CYP3A inhibitors increases elbasvir and grazoprevir concentrations. Co-administration of ZEPATIER™ with certain strong CYP3A inhibitors is not recommended (see **WARNINGS AND PRECAUTIONS**). Co-administration of ZEPATIER™ with P-gp inhibitors is expected to have a minimal effect on the plasma concentrations of ZEPATIER™.

Grazoprevir is a substrate of OATP1B drug transporters. Co-administration of ZEPATIER™ with drugs that inhibit OATP1B transporters may result in a significant increase in the plasma ZEPATIER™ concentration of grazoprevir. As such, co-administration of ZEPATIER™ with OATP1B inhibitors is contraindicated (see **CONTRAINDICATIONS**).

Effects of ZEPATIER™ on Other Drugs
Elbasvir and grazoprevir are inhibitors of the drug transporter breast cancer resistance protein (BCRP) at the intestinal level in humans and may increase plasma concentrations of co-administered BCRP substrates. Elbasvir is not a CYP3A inhibitor *in vitro* and grazoprevir is a weak, but not clinically relevant, CYP3A inhibitor in humans. Therefore, no dose adjustment is required for CYP3A substrates when co-administered with ZEPATIER™.

Grazoprevir is not a P-gp inhibitor *in vitro* and elbasvir has minimal intestinal P-gp inhibition in humans. Therefore, P-gp substrates may be administered without dose adjustment when co-administered with ZEPATIER™. Elbasvir and grazoprevir are not OATP1B inhibitors in humans. Clinically significant drug interactions with ZEPATIER™ as an inhibitor of other CYP enzymes, UGT1A1, and esterases (CES1, CES2, and CatA), are not expected. *In vitro*, elbasvir and grazoprevir did not induce CYP1A2, CYP2B6, or CYP3A.

Drug-Drug Interactions

Established and other Potential Drug Interactions
If dose adjustments of concomitant medications are made due to treatment with ZEPATIER™, doses should be readjusted after administration of ZEPATIER™ is completed.

Table 8 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either ZEPATIER™, the components of ZEPATIER™ (elbasvir [EBR] and grazoprevir [GZR]) as individual agents, or are predicted drug interactions that may occur with ZEPATIER™ (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS, Drug Interactions Studie**s).

Table 8 - Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions[Þ]

Concomitant Drug Class: Drug Name	Effect on Concentration[†]	Clinical Comment
Antifungals ketoconazole [‡]	↑ EBR ↑ GZR	Concomitant use of oral ketoconazole and ZEPATIER™ may increase the overall risk of hepatotoxicity; co-administration of ketoconazole is not recommended.
Endothelin Antagonist: bosentan	↓ EBR ↓ GZR	Co-administration of ZEPATIER™ with bosentan, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER™. Co-administration is not recommended.
Immunosuppressants: tacrolimus[‡]	↑ tacrolimus	Co-administration of ZEPATIER™ with systemic tacrolimus increases the concentrations of tacrolimus. Frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of co-administration is recommended.
HIV Medications:		
elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	↑ EBR ↑ GZR	Co-administration of ZEPATIER™ with the fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate increases the concentrations of EBR and GZR. Co-administration is not recommended.
etravirine	↓ EBR ↓ GZR	Co-administration of ZEPATIER™ with etravirine a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER™. Co-administration is not recommended.
HMG-CoA Reductase Inhibitors[#]:		
atorvastatin[‡]	↑ atorvastatin	Co-administration of EBR and GZR with atorvastatin increases the concentrations of atorvastatin. The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER™.[#]
rosuvastatin[‡]	↑ rosuvastatin	Co-administration of EBR and GZR and with rosuvastatin increases the concentrations of rosuvastatin. The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with ZEPATIER™.[#]
fluvastatin lovastatin simvastatin	↑ fluvastatin ↑ lovastatin ↑ simvastatin	Co-administration of ZEPATIER™ with these statins has not been studied but may increase the concentrations of these statins. The dose of fluvastatin, lovastatin, or simvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER™.[#]
Wakefulness-Promoting Agents: modafinil	↓ EBR ↓ GZR	Co-administration of ZEPATIER™ with modafinil, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER™. Co-administration is not recommended.

[Þ]This table is not all inclusive.
[†]↓ = decrease, ↑ = increase.
[‡] These interactions have been studied in healthy adults.
[#]See **DRUG INTERACTIONS**, section below: Drugs without Clinically Significant Interactions with

ZEPATIER™ for a list of HMG Co-A reductase inhibitors without clinically relevant interactions with ZEPATIER™.

Drugs without Clinically Significant Interactions with ZEPATIER™

The interaction between the components of ZEPATIER™ (elbasvir or grazoprevir) or ZEPATIER™ and the following drugs were evaluated in clinical studies, and no dose adjustments are needed when ZEPATIER™ is used with the following drugs individually: acid reducing agents (proton pump inhibitors, H2 blockers, antacids), buprenorphine/naloxone, digoxin, dolutegravir, methadone, mycophenolate mofetil, oral contraceptive pills, phosphate binders, pravastatin, prednisone, raltegravir, ribavirin, rilpivirine, tenofovir disoproxil fumarate, and sofosbuvir (see **DRUG INTERACTIONS, Drug Interactions Studies**).

No clinically relevant drug-drug interaction is expected when ZEPATIER™ is co-administered with abacavir, emtricitabine, entecavir, and lamivudine.

Drug Interaction Studies

Drug interaction studies were performed in healthy adults with elbasvir, grazoprevir, or co-administered elbasvir and grazoprevir and drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions. Table 9 summarizes the effects of co-administered drugs on the exposures of the individual components of ZEPATIER™ (elbasvir and grazoprevir). Table 10 summarizes the effects of the individual components of ZEPATIER™ on the exposures of the co-administered drugs. For information regarding clinical recommendations, see **WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS, Drug-Drug Interactions**.

Grazoprevir is a substrate of OATP1B. Co-administration of ZEPATIER™ with drugs that inhibit OATP1B transporters may result in a clinically relevant increase in grazoprevir plasma concentrations.

Elbasvir has minimal intestinal P-gp inhibition in humans, and does not result in clinically relevant increases in concentrations of digoxin (a P-gp substrate), with an 11% increase in plasma AUC (see Table 10). Grazoprevir is not a P-gp inhibitor *in vitro*. Therefore, P-gp substrates may be administered without dose adjustment when co-administered with ZEPATIER™.

Elbasvir and grazoprevir are inhibitors of the drug transporter breast cancer resistance protein (BCRP) at the intestinal level in humans and may increase plasma concentrations of co-administered BCRP substrates. Neither elbasvir nor grazoprevir are inhibitors of OATP1B in humans.

Clinically significant drug interactions with ZEPATIER™ as an inhibitor of other CYP enzymes, UGT1A1, and esterases (CES1, CES2, and CatA), are not expected. *In vitro*, elbasvir and grazoprevir did not induce CYP1A2, CYP2B6, or CYP3A. A clinical interaction study with montelukast confirmed that grazoprevir is not a CYP2C8 inhibitor (CYP isoform with lowest *in vitro* IC_{50}).

Table 9 - Drug Interactions: Changes in Pharmacokinetics of Elbasvir or Grazoprevir in the Presence of Co-Administered Drug

Co-Administered Drug	Regimen of Co-Administered Drug	Regimen of GZR or/and EBR	N	Geometric Mean Ratio [90% CI] of GZR and EBR PK with/without Co-Administered Drug (No Effect=1.00)			
					AUC[§]	C_{max}	C_{24}
Antifungal							
Ketoconazole	400 mg once daily	EBR 50 mg single-dose	7	EBR	1.80 (1.41, 2.29)	1.29 (1.00, 1.66)	1.89 (1.37, 2.60)
	400 mg once daily	GZR 100 mg single-dose	8	GZR	3.02 (2.42, 3.76)	1.13 (0.77, 1.67)	--
Antimycobacterial							
Rifampin	600 mg single-dose IV	EBR 50 mg single-dose	14	EBR	1.22 (1.06, 1.40)	1.41 (1.18, 1.68)	1.31 (1.12, 1.53)
	600 mg single-dose PO	EBR 50 mg single-dose	14	EBR	1.17 (0.98, 1.39)	1.29 (1.06, 1.58)	1.21 (1.03, 1.43)
	600 mg PO once daily	GZR 200 mg once daily	12	GZR	0.93 (0.75, 1.17)	1.16 (0.82, 1.65)	0.10 (0.07, 0.13)
	600 mg IV single-dose	GZR 200 mg single-dose	12	GZR	10.21 (8.68, 12.00)	10.94 (8.92, 13.43)	1.77 (1.40, 2.24)
	600 mg PO single-dose	GZR 200 mg once daily	12	GZR	8.35 (7.38, 9.45)[†]	6.52 (5.16, 8.24)	1.62 (1.32, 1.98)
HCV Antiretroviral							
EBR	20 mg once daily	GZR 200 mg once daily	10	GZR	0.90 (0.63, 1.28)	0.87 (0.50, 1.52)	0.94 (0.77, 1.15)
GZR	200 mg once daily	EBR 20 mg once daily	10	EBR	1.01 (0.83, 1.24)	0.93 (0.76, 1.13)	1.02 (0.83, 1.24)
HIV Protease Inhibitor							
Atazanavir/ ritonavir	300 mg/ 100 mg once daily	EBR 50 mg once daily	10	EBR	4.76 (4.07, 5.56)	4.15 (3.46, 4.97)	6.45 (5.51, 7.54)
	300 mg/ 100 mg once daily	GZR 200 mg once daily	12	GZR	10.58 (7.78, 14.39)	6.24 (4.42, 8.81)	11.64 (7.96, 17.02)
Darunavir/ ritonavir	600 mg/ 100 mg twice daily	EBR 50 mg once daily	10	EBR	1.66 (1.35, 2.05)	1.67 (1.36, 2.05)	1.82 (1.39, 2.39)
	600 mg/ 100 mg twice daily	GZR 200 mg once daily	13	GZR	7.50 (5.92, 9.51)	5.27 (4.04, 6.86)	8.05 (6.33, 10.24)
Lopinavir/ ritonavir	400 mg/ 100 mg twice daily	EBR 50 mg once daily	10	EBR	3.71 (3.05, 4.53)	2.87 (2.29, 3.58)	4.58 (3.72, 5.64)
	400 mg/ 100 mg	GZR 200 mg once daily	13	GZR	12.86 (10.25, 16.13)	7.31 (5.65, 9.45)	21.70 (12.99, 36.25)

	twice daily						
Ritonavir‡	100 mg twice daily	GZR 200 mg single-dose	10	GZR	2.03 (1.60, 2.56)	1.15 (0.60, 2.18)	1.88 (1.65, 2.14)
HIV Integrase Strand Transfer Inhibitor							
Dolutegravir	50 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	EBR	0.98 (0.93, 1.04)	0.97 (0.89, 1.05)	0.98 (0.93, 1.03)
	50 mg single-dose	EBR 50 mg once + GZR 200 mg once daily	12	GZR	0.81 (0.67, 0.97)	0.64 (0.44, 0.93)	0.86 (0.79, 0.93)
Raltegravir	400 mg single-dose	EBR 50 mg single-dose	10	EBR	0.81 (0.57, 1.17)	0.89 (0.61, 1.29)	0.80 (0.55, 1.16)
	400 mg twice daily	GZR 200 mg once daily	11	GZR	0.89 (0.72, 1.09)	0.85 (0.62, 1.16)	0.90 (0.82, 0.99)
HIV Non-Nucleoside Reverse Transcriptase Inhibitor							
Efavirenz	600 mg once daily	EBR 50 mg once daily	10	EBR	0.46 (0.36, 0.59)	0.55 (0.41, 0.73)	0.41 (0.28, 0.59)
	600 mg once daily	GZR 200 mg once daily	12	GZR	0.17 (0.13, 0.24)	0.13 (0.09, 0.19)	0.31 (0.25, 0.38)
Rilpivirine	25 mg once daily	EBR 50 mg + GZR 200 mg once daily	19	EBR	1.07 (1.00, 1.15)	1.07 (0.99, 1.16)	1.04 (0.98, 1.11)
	25 mg once daily	EBR 50 mg + GZR 200 mg once daily	19	GZR	0.98 (0.89, 1.07)	0.97 (0.83, 1.14)	1.00 (0.93, 1.07)
HIV Nucleotide Reverse Transcriptase Inhibitor							
Tenofovir disoproxil fumarate	300 mg once daily	EBR 50 mg once daily	10	EBR	0.93 (0.82, 1.05)	0.88 (0.77, 1.00)	0.92 (0.81, 1.05)
	300 mg once daily	GZR 200 mg once daily	12	GZR	0.86 (0.65, 1.12)	0.78 (0.51, 1.18)	0.89 (0.78, 1.01)
HIV regimen: Fixed Dose Regimen							
Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disproxil Fumarate	Elvitegravir 150 mg/ Cobicistat 150 mg/ Emtricitabine 200 mg/ 300 mg Tenofovir Disoproxil Fumarate once daily	EBR 50 mg / GZR 100 mg once daily	22	EBR	2.18 (2.02, 2.35)	1.91 (1.77, 2.05)	2.38 (2.19, 2.60)
		EBR 50 mg / GZR 100 mg once daily	22	GZR	5.36 (4.48, 6.43)	4.59 (3.70, 5.69)	2.78 (2.48, 3.11)
Immunosuppressant							
Cyclosporine	400 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.98 (1.84, 2.13)	1.95 (1.84, 2.07)	2.21 (1.98, 2.47)
	400 mg	EBR 50 mg +	14	GZR	15.21	17.00	3.39

	single-dose	GZR 200 mg + once daily			(12.83, 18.04)	(12.94, 22.34)	(2.82, 4.09)
Mycophenolate mofetil	1000 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.07 (1.00, 1.14)	1.07 (0.98, 1.16)	1.05 (0.97, 1.14)
	1000 mg single-dose	EBR 50 mg + GZR 200 mg + once daily	14	GZR	0.74 (0.60, 0.92)	0.58 (0.42, 0.82)	0.97 (0.89, 1.06)
Prednisone	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.17 (1.11, 1.24)	1.25 (1.16, 1.35)	1.04 (0.97, 1.12)
	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	1.09 (0.95, 1.25)	1.34 (1.10, 1.62)	0.93 (0.87, 1.00)
Tacrolimus	2 mg single-dose	EBR 50 mg + GZR 200 mg once daily	16	EBR	0.97 (0.90, 1.06)	0.99 (0.88, 1.10)	0.92 (0.83, 1.02)
	2 mg single-dose	EBR 50 mg + GZR 200 mg once daily	16	GZR	1.12 (0.97, 1.30)	1.07 (0.83, 1.37)	0.94 (0.87, 1.02)
Opioid-Substitution Therapy							
Buprenorphine/ naloxone	8 mg/2 mg single-dose	EBR 50 mg single-dose	15	EBR	1.22 (0.98, 1.52)	1.13 (0.87, 1.46)	1.22 (0.99, 1.51)
	8-24 mg/ 2-6 mg once daily	GZR 200 mg once daily	12	GZR	0.80 (0.53, 1.22)	0.76 (0.40, 1.44)	0.69 (0.54, 0.88)
Methadone	20-120 mg once daily	EBR 50 mg once daily	10	EBR	1.71 (1.16, 2.51)	1.93 (1.30, 2.86)	1.86 (1.22, 2.83)
	20-150 mg once daily	GZR 200 mg once daily	12	GZR	1.03 (0.53, 1.97)	0.88 (0.36, 2.14)	0.77 (0.56, 1.04)
Acid-Reducing Agent							
Famotidine	20 mg single-dose	EBR 50 mg / GZR 100 mg single-dose	16	EBR	1.05 (0.92, 1.18)	1.11 (0.98, 1.26)	1.03 (0.91, 1.17)
	20 mg single-dose	EBR 50 mg/ GZR 100 mg single-dose	16	GZR	1.10 (0.95, 1.28)	0.89 (0.71, 1.11)	1.12 (0.97, 1.30)
Pantoprazole	40 mg once daily	EBR 50 mg / GZR 100 mg single-dose	16	EBR	1.05 (0.93, 1.18)	1.02 (0.92, 1.14)	1.03 (0.92, 1.17)
	40 mg once daily	EBR 50 mg/ GZR 100 mg single-dose	16	GZR	1.12 (0.96, 1.30)	1.10 (0.89, 1.37)	1.17 (1.02, 1.34)
Phosphate Binder							
Calcium acetate	2668 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	EBR	0.92 (0.75, 1.14)	0.86 (0.71, 1.04)	0.87 (0.70, 1.09)
	2668 mg single-dose	EBR 50 mg + GZR 100 mg	12	GZR	0.79 (0.68, 0.91)	0.57 (0.40, 0.83)	0.77 (0.61, 0.99)

		single-dose					
Sevelamer carbonate	2400 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	EBR	1.13 (0.94, 1.37)	1.07 (0.88, 1.29)	1.22 (1.02, 1.45)
	2400 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	GZR	0.82 (0.68, 0.99)	0.53 (0.37, 0.76)	0.84 (0.71, 0.99)
Statin							
Atorvastatin	20 mg single-dose	GZR 200 mg once daily	9	GZR	1.26 (0.97, 1.64)	1.26 (0.83, 1.90)	1.11 (1.00, 1.23)
Pravastatin	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	EBR	0.98 (0.93, 1.02)	0.97 (0.89, 1.05)	0.97 (0.92, 1.02)
	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	GZR	1.24 (1.00, 1.53)	1.42 (1.00, 2.03)	1.07 (0.99, 1.16)
Rosuvastatin	10 mg single-dose	EBR 50 mg + GZR 200 mg single-dose	11	EBR	1.09 (0.98, 1.21)	1.11 (0.99, 1.26)	0.96 (0.86, 1.08)
	10 mg single-dose	GZR 200 mg once daily	11	GZR	1.16 (0.94, 1.44)	1.13 (0.77, 1.65)	0.93 (0.84, 1.03)
	10 mg single-dose	EBR 50 mg + GZR 200 mg once daily	11	GZR	1.01 (0.79, 1.28)	0.97 (0.63, 1.50)	0.95 (0.87, 1.04)

Abbreviations: EBR, elbasvir; GZR, grazoprevir; IV, intravenous; PO, oral; EBR+GZR, administration of GZR and EBR as separate pills; EBR/GZR, administration of EBR and GZR as a single fixed-dose combination tablet

[§] $AUC_{0\text{-}inf}$ for single-dose, $AUC_{0\text{-}24}$ for once daily

[†] $AUC_{0\text{-}24}$

[‡] Higher doses of ritonavir have not been tested in a drug interaction study with GZR

Table 10 - Drug Interactions: Changes in Pharmacokinetics for Co-Administered Drug in the Presence of Elbasvir, Grazoprevir, or Co-Administered Elbasvir and Grazoprevir

Co-Administered Drug	Regimen of Co-Administered Drug	EBR or/and GZR Administration	EBR or/and GZR Regimen	N	Geometric Mean Ratio [90% CI] of Co-Administered Drug PK with/without EBR or/and GZR (No Effect=1.00)		
					AUC[§]	C_{max}	C_{trough}[†]
P-gp Substrate							
Digoxin	Digoxin 0.25 mg single-dose	EBR	50 mg once daily	18	1.11 (1.02, 1.22)	1.47 (1.25, 1.73)	--
CYP3A Substrate							
Midazolam	Midazolam 2 mg single-dose	GZR	200 mg once daily	11	1.34 (1.29, 1.39)	1.15 (1.01, 1.31)	--
CYP2C8 Substrate							
Montelukast	Montelukast 10 mg single-dose	GZR	200 mg once daily	23	1.11 (1.01, 1.20)	0.92 (0.81, 1.06)	1.39 (1.25, 1.56)

HCV Antiretroviral							
GS-331007	Sofosbuvir 400 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	1.13 (1.05, 1.21)	0.87 (0.78, 0.96)	1.53 (1.43, 1.63)
Sofosbuvir	Sofosbuvir 400 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	2.43 (2.12, 2.79)‡	2.27 (1.72, 2.99)	--
HIV Protease Inhibitor							
Atazanavir/ ritonavir	Atazanavir 300 mg/ ritonavir 100 mg once daily	EBR	50 mg once daily	8	1.07 (0.98, 1.17)	1.02 (0.96, 1.08)	1.15 (1.02, 1.29)
	Atazanavir 300 mg/ ritonavir 100 mg once daily	GZR	200 mg once daily	11	1.43 (1.30, 1.57)	1.12 (1.01, 1.24)	1.23 (1.13, 1.34)
Darunavir/ ritonavir	Darunavir 600 mg/ ritonavir 100 mg twice daily	EBR	50 mg once daily	8	0.95 (0.86, 1.06)	0.95 (0.85, 1.05)	0.94 (0.85, 1.05)
	Darunavir 600 mg/ ritonavir 100 mg twice daily	GZR	200 mg once daily	13	1.11 (0.99, 1.24)	1.10 (0.96, 1.25)	1.00 (0.85, 1.18)
Lopinavir/ ritonavir	Lopinavir 400 mg/ ritonavir 100 mg twice daily	EBR	50 mg once daily	9	1.02 (0.93, 1.13)	1.02 (0.92, 1.13)	1.07 (0.97, 1.18)
	Lopinavir 400 mg/ ritonavir 100 mg twice daily	GZR	200 mg once daily	13	1.03 (0.96, 1.16)	0.97 (0.88, 1.08)	0.97 (0.81, 1.15)
HIV Integrase Strand Transfer Inhibitor							
Dolutegravir	Dolutegravir 50 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	1.16 (1.00, 1.34)	1.22 (1.05, 1.40)	1.14 (0.95, 1.36)
Raltegravir	Raltegravir 400 mg single-dose	EBR	50 mg single-dose	10	1.02 (0.81, 1.27)	1.09 (0.83, 1.44)	0.99 (0.80, 1.22)§
	Raltegravir 400 mg twice daily	GZR	200 mg once daily	11	1.43 (0.89, 2.30)	1.46 (0.78, 2.73)	1.47 (1.09, 2.00)
HIV Non-Nucleoside Reverse Transcriptase Inhibitor							
Efavirenz	Efavirenz 600 mg once daily	EBR	50 mg once daily	7	0.82 (0.78, 0.86)	0.74 (0.67, 0.82)	0.91 (0.87, 0.96)
	Efavirenz 600 mg once daily	GZR	200 mg once daily	11	1.00 (0.96, 1.05)	1.03 (0.99, 1.08)	0.93 (0.88, 0.98)
Rilpivirine	Rilpivirine 25 mg once	EBR + GZR	50 mg + 200 mg once daily	19	1.13	1.07	1.16

	daily				(1.07, 1.20)	(0.97, 1.17)	(1.09, 1.23)
HIV Nucleotide Reverse Transcriptase Inhibitor							
Tenofovir disoproxil fumarate	Tenofovir disoproxil fumarate 300 mg once daily	EBR	50 mg once daily	10	1.34 (1.23, 1.47)	1.47 (1.32, 1.63)	1.29 (1.18, 1.41)
	Tenofovir disoproxil fumarate 300 mg once daily	GZR	200 mg once daily	12	1.18 (1.09, 1.28)	1.14 (1.04, 1.25)	1.24 (1.10, 1.39)
HIV regimen: Fixed Dose Regimen							
Elvitegravir	Elvitegravir 150 mg/ Cobicistat 150 mg/ Emtricitabine 200 mg/ 300 mg/ Tenofovir Disoproxil Fumarate once daily	EBR / GZR	50 mg / 100 mg once daily	22	1.10 (1.00, 1.21)	1.02 (0.93, 1.11)	1.31 (1.11, 1.55)
Cobicistat		EBR / GZR	50 mg / 100 mg once daily	22	1.49 (1.42, 1.57)	1.39 (1.29, 1.50)	--
Emtricitabine		EBR / GZR	50 mg / 100 mg once daily	22	1.07 (1.03, 1.10)	0.96 (0.90, 1.02)	1.19 (1.13, 1.25)
Tenofovir disoproxil fumarate		EBR / GZR	50 mg / 100 mg once daily	22	1.18 (1.13, 1.24)	1.25 (1.14, 1.37)	1.20 (1.15, 1.26)
Immunosuppressant							
Cyclosporine	Cyclosporine 400 mg single-dose	EBR + GZR	200 mg + 50 mg once daily	14	0.96 (0.90, 1.02)	0.90 (0.85, 0.97)	1.00 (0.92, 1.08)[§]
Mycophenolic acid	Mycophenolate mofetil 1000 mg single-dose	EBR + GZR	200 mg + 50 mg once daily	14	0.95 (0.87, 1.03)	0.85 (0.67, 1.07)	--
Prednisolone	Prednisone 40 mg single-dose	EBR + GZR	200 mg + 50 mg once daily	14	1.08 (1.01, 1.16)	1.04 (0.99, 1.09)	--
Prednisone	Prednisone 40 mg single-dose	EBR + GZR	200 mg + 50 mg once daily	14	1.08 (1.00, 1.17)	1.05 (1.00, 1.10)	--
Tacrolimus	Tacrolimus 2 mg single-dose	EBR + GZR	200 mg + 50 mg once daily	16	1.43 (1.24, 1.64)	0.60 (0.52, 0.69)	1.70 (1.49, 1.94)[§]
Oral Contraceptive							
Ethinyl estradiol (EE)	0.03 mg EE/ 0.15 mg LNG single-dose	EBR	50 mg once daily	20	1.01 (0.97, 1.05)	1.10 (1.05, 1.16)	--
Levonorgestrel (LNG)		EBR	50 mg once daily	20	1.14 (1.04, 1.24)	1.02 (0.95, 1.08)	--
		GZR	200 mg once daily	20	1.10 (1.05, 1.14)	1.05 (0.98, 1.12)	--
		GZR	200 mg once daily	20	1.23 (1.15, 1.32)	0.93 (0.84, 1.03)	--

Opioid Substitution Therapy							
Buprenorphine	Buprenorphine 8 mg/Naloxone 2 mg single-dose	EBR	50 mg once daily	15	0.98 (0.89, 1.08)	0.94 (0.82, 1.08)	0.98 (0.88, 1.09)
	Buprenorphine 8-24 mg/ Naloxone 2-6 mg once daily	GZR	200 mg once daily	12	0.98 (0.81, 1.19)	0.90 (0.76, 1.07)	--
R-Methadone	Methadone 20-120 mg once daily	EBR	50 mg once daily	10	1.03 (0.92, 1.15)	1.07 (0.95, 1.20)	1.10 (0.96, 1.26)
	Methadone 20-150 mg once daily	EBR	50 mg once daily	10	1.09 (0.94, 1.26)	1.09 (0.95, 1.25)	1.20 (0.98, 1.47)
S-Methadone	Methadone 20-120 mg once daily	GZR	200 mg once daily	12	1.09 (1.02, 1.17)	1.03 (0.96, 1.11)	--
	Methadone 20-150 mg once daily	GZR	200 mg once daily	12	1.23 (1.12, 1.35)	1.15 (1.07, 1.25)	--
Statin							
Atorvastatin	Atorvastatin 10 mg single-dose	EBR + GZR	50 mg once + 200 mg daily	16	1.94 (1.63, 2.33)	4.34 (3.10, 6.07)	0.21 (0.17, 0.26)
	Atorvastatin 20 mg single-dose	GZR	200 mg once daily	9	3.00 (2.42, 3.72)	5.66 (3.39, 9.45)	--
Pravastatin	Pravastatin 40 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	1.33 (1.09, 1.64)[¶]	1.28 (1.05, 1.55)	--
Rosuvastatin	Rosuvastatin 10 mg single-dose	EBR + GZR +	50 mg + 200 mg + once daily	12	2.26 (1.89, 2.69)[#]	5.49 (4.29, 7.04)	0.98 (0.84, 1.13)
		GZR	200 mg once daily	12	1.59 (1.33, 1.89)[#]	4.25 (3.25, 5.56)	0.80 (0.70, 0.91)

Abbreviations: EBR, elbasvir; GZR, grazoprevir; EBR+GZR, administration of EBR and GZR as separate tablets

[§] $AUC_{0\text{-}inf}$ for single-dose administration; $AUC_{0\text{-}24}$ for once daily administration; $AUC_{0\text{-}12}$ for twice daily administration

[†] C_{24} for once daily administration; C_{12} for twice daily administration

[‡] N=14

[§] C_{12}

[¶] N=10

[#] N=8

Drug-Food Interactions

ZEPATIER™ can be taken with or without food.

Drug-Herb Interactions
Co-administration of ZEPATIER™ with St. John's Wort (Hypericum perforatum) is contraindicated.

Drug-Laboratory Interactions
Interactions with clinical laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Since ZEPATIER™ is a fixed dose combination product, an adjustment of its recommended dose is not possible.

Recommended Dose Regimens in Adults
ZEPATIER™ is a two-drug, fixed-dose combination product containing 50 mg of elbasvir and 100 mg of grazoprevir in a single tablet. The recommended dosage of ZEPATIER™ is one tablet taken orally once daily with or without food (see **Table 11** and **ACTION AND CLINICAL PHARMACOLOGY**). Dose adjustment cannot be made for this fixed dose combination.

Treatment Regimen and Duration of Therapy

Table 11 below provides the recommended ZEPATIER™ treatment regimen and duration based on the patient population and genotype in HCV mono-infected.

Table 11 - Recommended Dosage Regimens and Durations for ZEPATIER™ for Treatment of Chronic Hepatitis C Infection in Patients with or without Cirrhosis

Treatment[þ]	Duration
Genotype 1 or 4 TN[&] or PR-TE[ß] Relapsers; Genotype 1 PI/PR-TE* Relapsers	
ZEPATIER™	12 weeks *(8 weeks may be considered in treatment-naïve genotype 1b[†] patients without significant fibrosis or cirrhosis[‡])*
Genotype 1 PR-TE or PI/PR-TE On-Treatment Virologic Failures[§] **Genotype 4 PR-TE On-Treatment Virologic Failures**	
Genotype 1b[†] (PR-TE or PI/PR-TE) ZEPATIER™	12 weeks
Genotype 1a (PR-TE or PI/PR-TE), or Genotype 4 (PR-TE) ZEPATIER™ with ribavirin[¶,#]	16 weeks
Genotype 3 TN	
ZEPATIER™ with sofosbuvir[$]	12 weeks

[þ]Refer to the product monograph of the medicinal products that are used in combination with ZEPATIER™ for specific dosing instructions.
[&]TN:Treatment-naïve.
[ß]PR-TE: Patients who failed treatment with peginterferon alfa + ribavirin.
*PI/PR-TE: Patients who failed peginterferon alfa + ribavirin + boceprevir, simeprevir, or telaprevir.
[†]Includes patients with known genotype 1 subtypes other than 1a or 1b.
[‡]Patients without clinically significant fibrosis or cirrhosis as determined by liver biopsy (i.e., METAVIR F0-F2) or by non-invasive tests.
[§]On-treatment virologic failures are patients who have had a null response, partial response, virologic breakthrough or rebound, or intolerance to prior treatment.
[¶]In clinical trials, the dose of ribavirin was weight-based (<66 kg = 800 mg/day, 66 to 80 kg = 1000 mg/day, 81 to 105 kg = 1200 mg/day, >105 kg = 1400 mg/day) administered in two divided doses with food. For further information on ribavirin dosing and dose modifications, refer to the ribavirin prescribing information.
[#]Patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73 m^2) or with end stage renal disease (ESRD) should receive ZEPATIER™ 12 weeks without ribavirin (See DOSAGE AND ADMINISTRATION, Severe Renal Impairment and ESRD).
[$]See Severe Renal impairment and end stage renal disease (ESRD).

HCV/HIV 1 Co infection

Safety and efficacy of ZEPATIER™ have been established in HIV-1 co-infected treatment-naïve HCV genotype 1 and 4 patients as well as treatment-experienced HCV genotype 1 patients. Dosing recommendation for these patients is same as in Table 11.

Severe Renal Impairment and ESRD

In genotype 1 patients with severe renal impairment (eGFR) < 30 mL/min/1.73m^2) or with ESRD, including patients on hemodialysis, administer ZEPATIER™ without ribavirin according to the treatment durations in Table 11 (see **WARNINGS AND PRECAUTIONS**, **Special**

Populations). For treatment-experienced genotype 1a patients with prior on-treatment virologic failure and severe renal impairment or with ESRD, 12 weeks without ribavirin treatment duration of ZEPATIER™ may be considered (see **CLINICAL TRIALS**).

The safety and efficacy of ZEPATIER™ in genotype 4 patients as well as ZEPATIER™ with sofosbuvir in genotype 3 patients with severe renal impairment (eGFR) <30 mL/min/1.73m^2) or with ESRD, including patients on hemodialysis have not been established.

Hepatic Impairment
ZEPATIER™ may be used as recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER™ is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B and C) due to the expected significant increase in grazoprevir plasma concentration (see **CONTRAINDICATIONS, WARNING AND PRECAUTIONS, Hepatic, and ACTION AND CLINICAL PHARMACOLOGY**).

The safety and efficacy of ZEPATIER™ have not been established in patients awaiting liver transplant or in liver transplant recipients. The plasma concentration of grazoprevir is increased if ZEPATIER™ is co-administered with cyclosporine. Co-administration with cyclosporine is contraindicated (see **DRUG INTERACTIONS**).

HCV/HBV (Hepatitis B Virus) co-infection
The safety and efficacy of ZEPATIER™ have not been studied in HCV/HBV co-infected patients.

Missed Dose
In case a dose of ZEPATIER™ is missed and it is within 16 hours of the time ZEPATIER™ is usually taken, the patient should be instructed to take ZEPATIER™ as soon as possible and then take the next dose of ZEPATIER™ at the usual time. If more than 16 hours have passed since ZEPATIER™ is usually taken, then the patient should be instructed that the missed dose should NOT be taken and to take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Human experience of overdose with ZEPATIER™ is limited. No specific antidote is available for overdose with ZEPATIER™. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

Hemodialysis does not remove elbasvir or grazoprevir since elbasvir and grazoprevir are highly bound to plasma protein (see **ACTION AND CLINICAL PHARMACOLOGY**).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Elbasvir is an HCV NS5A inhibitor and grazoprevir is an HCV NS3/4A protease inhibitor

ZEPATIER™ is a fixed-dose combination of elbasvir and grazoprevir which are direct-acting antiviral agents against the hepatitis C virus (see **MICROBIOLOGY**).

Pharmacodynamics
Cardiac Electrophysiology
Thorough QT studies have been conducted for elbasvir and grazoprevir..

The effect of elbasvir 700 mg on the QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) 3-period crossover thorough QT trial in 42 healthy subjects. At a plasma concentration 3 to 4 times the plasma therapeutic concentration, elbasvir does not prolong QTc to any clinically relevant extent.

The effect of grazoprevir 1600 mg on QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) 3-period crossover thorough QT trial in 41 healthy subjects. At a plasma concentration 40 times the therapeutic plasma concentration, grazoprevir does not prolong QTc to any clinically relevant extent.

Pharmacokinetics

Table 12 - Summary of ZEPATIER™'s Pharmacokinetic Parameters in Non-Cirrhotic, HCV-Infected Subjects

	C_{max}	AUC_{0-24h}
Elbasvir		
Steady-state geometric mean	137 nM	2180 nM•hr
Grazoprevir		
Steady-state geometric mean	220 nM	1860 nM•hr

The pharmacokinetic properties of elbasvir and grazoprevir have been evaluated in non-HCV-infected adult subjects and in HCV-infected adult subjects. Elbasvir pharmacokinetics were similar in healthy subjects and HCV-infected subjects and were approximately dose-proportional over the range of 5-100 mg once daily. Grazoprevir oral exposures are approximately 2-fold greater in HCV-infected subjects as compared to healthy subjects. Grazoprevir pharmacokinetics increased in a greater than dose-proportional manner over the range of 10-800 mg once daily in HCV-infected subjects. Ribavirin or sofosbuvir co-administration with ZEPATIER™ had no clinically relevant impact on plasma AUC and C_{max} of elbasvir and grazoprevir compared to administration of ZEPATIER™ alone. Following once daily administration of ZEPATIER™ to HCV-infected subjects, elbasvir and grazoprevir reached steady state within approximately 6 days.

Absorption:
Following administration of ZEPATIER™ to HCV-infected subjects, elbasvir peak plasma concentrations occur at a median T_{max} of 3 hours (range of 3 to 6 hours); grazoprevir peak plasma concentrations occur at a median T_{max} of 2 hours (range of 30 minutes to 3 hours).

Effect of Food
Relative to fasting conditions, the administration of a single dose of ZEPATIER™ with a high-fat (900 kcal, 500 kcal from fat) meal to healthy subjects resulted in increases in grazoprevir $AUC_{0\text{-}inf}$ and C_{max} of approximately 1.5-fold and 2.8-fold, respectively, and decreases in elbasvir $AUC_{0\text{-}inf}$ and C_{max} of approximately 11% and 15%, respectively. These differences in elbasvir and grazoprevir exposure are not clinically relevant; therefore, ZEPATIER™ may be taken without regard to food.

Distribution:
Elbasvir and grazoprevir are extensively bound (>99.9% and 98.8%, respectively) to human plasma proteins. Both elbasvir and grazoprevir bind to human serum albumin and α1-acid glycoprotein. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

In preclinical distribution studies, elbasvir distributed into most tissues including the liver and grazoprevir distributed predominantly to the liver.

Metabolism:
Elbasvir and grazoprevir are partially eliminated by oxidative metabolism, primarily by CYP3A. No circulating metabolites of either elbasvir or grazoprevir were detected in human plasma.

Elimination:
The geometric mean apparent terminal half-life (% geometric mean coefficient of variation) is approximately 24 (24%) hours at 50 mg elbasvir and approximately 31 (34%) hours at 100 mg grazoprevir and in HCV-infected subjects.

The primary route of elimination of elbasvir and grazoprevir is through feces with almost all (>90%) of radiolabeled dose recovered in feces compared to <1% in urine.

Special Populations and Conditions
Pediatrics*:*
The pharmacokinetics of ZEPATIER™ in pediatric patients less than 18 years of age have not been established.

Geriatrics:
In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 14% and 72% higher, respectively, in >65-year-old subjects compared to young subjects. These changes are not clinically relevant; therefore, no dose adjustment of ZEPATIER™ is recommended based on age (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Gender:
In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 50% and 30% higher, respectively, in females compared to males. These changes are not clinically relevant; therefore, no dose adjustment of ZEPATIER™ is recommended based on sex.

Weight/BMI:
In population pharmacokinetic analyses, there was no effect of weight on elbasvir pharmacokinetics. Grazoprevir AUC is estimated to be 15% higher in subjects who are < 53 kg. This change is not clinically relevant for grazoprevir. Therefore, no dose adjustment of ZEPATIER™ is recommended based on weight/BMI.

Race/Ethnicity:
In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 15% and 50% higher, respectively, for Asians compared to Whites. Population pharmacokinetics estimates of exposure of elbasvir and grazoprevir were comparable between Whites and Black/African Americans. These changes are not clinically relevant; therefore, no dose adjustment of ZEPATIER™ is recommended based on race/ethnicity.

Hepatic Insufficiency:
The pharmacokinetics of elbasvir and grazoprevir were evaluated in non-HCV-infected subjects with mild hepatic impairment (Child-Pugh Category A [CP-A], score of 5-6), moderate hepatic impairment (Child-Pugh Category B [CP-B], score of 7-9) and severe hepatic impairment (Child-Pugh Category C [CP-C], score of 10-15). In addition, the pharmacokinetics of elbasvir and grazoprevir were also evaluated in HCV-infected subjects with mild hepatic impairment (CP-A) or moderate hepatic impairment (CP-B).

Elbasvir $AUC_{0\text{-}inf}$ was decreased by 40% in non-HCV-infected subjects with mild hepatic impairment compared to matching healthy subjects. Population PK analyses of HCV-infected subjects in Phase 2 and 3 studies demonstrated that grazoprevir steady-state $AUC_{0\text{-}24}$ increased by approximately 65% in subjects with compensated cirrhosis compared to non-cirrhotic subjects. Elbasvir steady-state AUC was similar in HCV-infected subjects with mild hepatic impairment compared to subjects without hepatic impairment. In non-HCV-infected subjects with CP-A mild hepatic impairment, grazoprevir steady-state $AUC_{0\text{-}24}$ was increased 70% compared to matching healthy subjects.

Compared to healthy matched subjects, elbasvir AUC decreased by 28% in non-HCV-infected subjects with moderate hepatic impairment compared to matched healthy subjects. Elbasvir steady-state AUC was similar in HCV-infected subjects with moderate hepatic impairment compared to subjects without hepatic impairment. Grazoprevir steady-state $AUC_{0\text{-}24}$ was increased 5-fold in non-HCV-infected subjects with moderate hepatic impairment (CP-B). ZEPATIER™ is contraindicated in HCV-infected subjects with moderate hepatic impairment (Child-Pugh B) due to lack of clinical safety and efficacy experience in this population and the expected increase in grazoprevir exposure.

Elbasvir $AUC_{0\text{-}inf}$ is decreased by 12% in non-HCV-infected subjects with severe hepatic impairment compared to matching healthy subjects. Grazoprevir steady-state $AUC_{0\text{-}24}$ was

increased 12-fold in non-HCV-infected subjects with severe hepatic impairment (CP-C) compared to healthy matched subjects. ZEPATIER™ is contraindicated in HCV-infected subjects with severe hepatic impairment (Child-Pugh C) based on the significant increase in grazoprevir exposure observed in non-HCV-infected subjects with severe hepatic impairment (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Population**s).

Renal Insufficiency:
The pharmacokinetics of elbasvir and grazoprevir were evaluated in non-HCV-infected subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) with or without hemodialysis and also in HCV-infected subjects with severe renal impairment with or without hemodialysis. Elbasvir and grazoprevir are not expected to be removed by peritoneal dialysis as both are highly protein bound.

Relative to non-HCV-infected subjects with normal renal function (eGFR >80 mL/min/1.73 m^2), elbasvir and grazoprevir AUC values were increased by 86% and 65%, respectively, in non-HCV-infected subjects with severe renal impairment who were not on hemodialysis. Relative to subjects with normal renal function, elbasvir and grazoprevir AUC values were unchanged in non-HCV-infected subjects with hemodialysis-dependent, severe renal impairment. Elbasvir and grazoprevir are highly bound to plasma protein. Elbasvir and grazoprevir are not removed by hemodialysis. Concentrations of elbasvir were not quantifiable in the dialysate samples. Less than 0.5% of grazoprevir was recovered in dialysate over a 4-hour hemodialysis session. Elbasvir and grazoprevir are not expected to be removed by peritoneal dialysis.

In population pharmacokinetic analysis, elbasvir AUC was 25% higher in hemodialysis-dependent subjects and 46% higher in non-hemodialysis-dependent subjects with severe renal impairment compared to elbasvir AUC in subjects without severe renal impairment. In population pharmacokinetic analysis in HCV-infected subjects, grazoprevir AUC was 10% higher in hemodialysis-dependent subjects and 40% higher in non-hemodialysis-dependent subjects with severe renal impairment compared to grazoprevir AUC in subjects without severe renal impairment.

Overall, changes in exposure of elbasvir and grazoprevir in HCV-infected subjects with renal impairment with or without hemodialysis are not clinically relevant. (see **WARNINGS AND PRECAUTIONS, Special Populations**).

STORAGE AND STABILITY
Store at room temperature (15°C - 30°C) in the original package.

Store ZEPATIER™ in the original blister package until use to protect from moisture.

SPECIAL HANDLING INSTRUCTIONS
No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

ZEPATIER™ (elbasvir and grazoprevir) is a fixed-dose combination tablet containing 50 mg of elbasvir and100 mg of grazoprevir and for oral administration. The film-coated tablets are beige-colored, oval-shaped, debossed with "770" on one side and plain on the other. They are available in two blister packages totaling 28 tablets.

Composition

ZEPATIER™ film-coated tablets contain 50 mg of elbasvir and 100 mg of grazoprevir).

Non-medicinal ingredients**:** colloidal silicon dioxide, copovidone, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, sodium chloride, sodium lauryl sulfate, and vitamin E polyethylene glycol succinate.

The tablets are film-coated with a coating material containing the following inactive ingredients: carnauba wax, ferrosoferric oxide, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide and triacetin.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

ZEPATIER™ (elbasvir and grazoprevir) tablets

Drug Substance

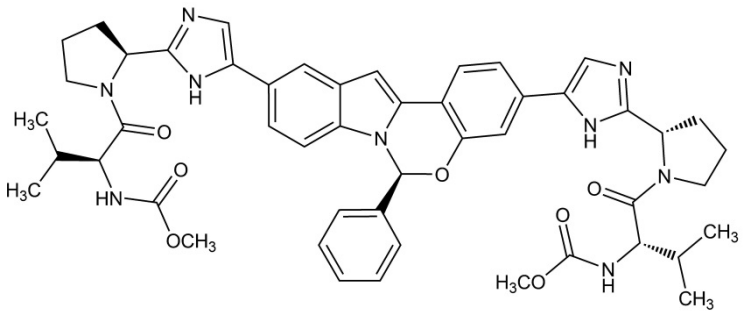
Elbasvir:

Proper name: elbasvir

Chemical name: Dimethyl *N*,*N*′-([(6*S*)-6-phenylindolo[1,2-*c*][1,3]benzoxazine-3,10-diyl]bis{1*H*-imidazole-5,2-diyl-(2*S*)-pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})dicarbamate.

Molecular formula and molecular mass: $C_{49}H_{55}N_9O_7$; 882.02

Structural formula:



Physicochemical properties: Elbasvir is practically insoluble in water (<0.1 mg/mL) and very slightly soluble in ethanol (0.2 mg/mL), but is very soluble in ethyl acetate and acetone.

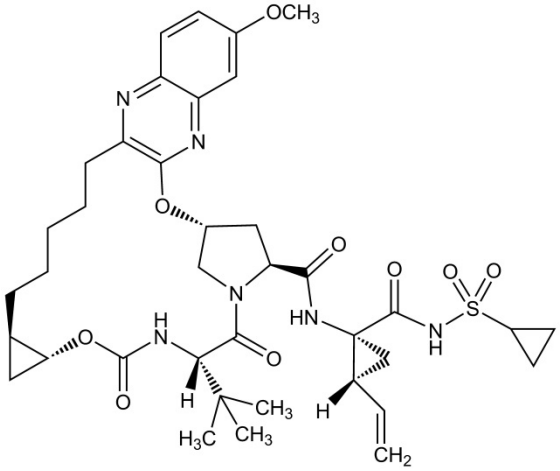
Grazoprevir:

Proper name: grazoprevir

Chemical name: 1a*R*,5*S*,8*S*,10*R*,22a*R*)-*N*-[(1*R*,2*S*)-1-[(Cyclopropylsulfonamido)carbonyl]-2-ethenylcyclopropyl]-14-methoxy-5-(2-methylpropan-2-yl)-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide.

Molecular formula and molecular mass: $C_{38}H_{50}N_6O_9S$; 766.90

Structural formula:



Physicochemical properties: Grazoprevir is practically insoluble in water (< 0.1 mg/mL) but is freely soluble in ethanol and some organic solvents (e.g., acetone, tetrahydrofuran and N,N-dimethylformamide).

CLINICAL TRIALS

Overview of Clinical Trials

The safety and efficacy of ZEPATIER™ (elbasvir + grazoprevir FDC) were evaluated in 8 clinical trials in approximately1800 subjects with genotype (GT) 1, 3, or 4 chronic hepatitis C (CHC) infection with compensated liver disease (with and without cirrhosis).

An overview of the trials is provided in Table 13.

Table 13 - Summary of Clinical Trial Designs in Treatment of Chronic Hepatitis C Infection

Trial	Population	Study Arms and Duration (Number of Subjects Treated)	Trial Design
C-EDGE TN (P060)	GT 1, 4 TN with or without cirrhosis	• ZEPATIER™ for 12 weeks (N=306) • Pbo for 12 weeks (N=105)	Randomized, double-blind, Pbo-controlled trial in TN subjects with GT 1, or 4 infection with or without cirrhosis. Subjects were randomized in a 3:1 ratio to: ZEPATIER™ for 12 weeks (ITG) or Pbo for 12 weeks followed by open-label treatment with ZEPATIER™ for 12 weeks (DTG).
C-EDGE COINFECTION (P061)	GT 1, 4 TN with or without cirrhosis HCV/HIV-1 co-infection	ZEPATIER™ for 12 weeks (N=217)	Open-label trial in TN HCV/HIV-1 co-infected subjects with GT 1, or 4 infection with or without cirrhosis. Subjects received ZEPATIER™ for 12 weeks.
C-SURFER (P052)	GT 1 TN or TE with or without cirrhosis Chronic Kidney Disease	• EBR[¶] + GZR[¶] for 12 weeks (N=122) • Pbo for 12 weeks (N=113)	Randomized, double-blind, Pbo-controlled trial in subjects with GT 1 infection, with or without cirrhosis, with CKD Stage 4 (eGFR 15-29 mL/min/1.73 m^2) or Stage 5 (eGFR < 15 mL/min/1.73 m^2), including subjects on hemodialysis, who were TN or who had failed prior therapy with IFN or peg-IFN ± RBV therapy. Subjects were randomized in a 1:1 ratio to one of the following treatment groups: EBR + GZR for 12 weeks (ITG) or Pbo for 12 weeks followed by open-label treatment with EBR + GZR for 12 weeks (DTG). In addition, 11 subjects received open-label EBR + GZR for 12 weeks (intensive PK arm).
C-WORTHY (P035)	GT 1, 3 TN with or without cirrhosis TE Null Responder with or without cirrhosis TN HCV/HIV-1 co-infection without cirrhosis	• EBR[¶]+ GZR[¶] for 8, 12, or 18 weeks (N=136, 31, and 63, respectively) • EBR[¶] + GZR[¶] + RBV[†] for 8, 12, or 18 weeks (N=152, 60, and 65, respectively)	Multi-arm, multi-stage, randomized, open-label trial which included subjects with GT 1 or 3 infection who were TN or who had failed prior therapy with peg-IFN ± RBV therapy. In the stage evaluating shorter duration of therapy in subjects with GT 1b infection without cirrhosis, subjects were randomized in a 1:1 ratio to EBR + GZR with or without RBV for 8 weeks. In the stage evaluating subjects with GT 3 infection without cirrhosis who were TN, subjects were randomized to EBR + GZR with RBV for 12 or 18 weeks. In the other stages, subjects with GT 1 infection with or without cirrhosis who were TN (with or

			without HCV/HIV-1 co-infection) or who were peg-IFN + RBV null responders, were randomized to EBR + GZR with or without RBV for 8, 12 or 18 weeks.
C-SCAPE (P047)	GT 4 TN without cirrhosis	• EBR[¶] + GZR[¶] for 12 weeks (N=10) EBR[¶] + GZR[¶] + RBV[†] for 12 weeks (N=10)	Randomized, open-label trial which included TN subjects with genotype 4 infection without cirrhosis. Subjects were randomized in a 1:1 ratio to EBR + GZR for 12 weeks or EBR + GZR + RBV for 12 weeks
C-EDGE TE (P068)	GT 1, 4 TE with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER™ for 12 or 16 weeks (N=105, and101, respectively) ZEPATIER™ + RBV[†] for 12 or 16 weeks (N=104 and104, respectively)	Randomized, open-label trial in subjects with GT 1, or 4 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior therapy with peg-IFN + RBV therapy. Subjects were randomized in a 1:1:1:1 ratio to one of the following treatment groups: ZEPATIER™ for 12 weeks, ZEPATIER™ + RBV for 12 weeks, ZEPATIER™ for 16 weeks, or ZEPATIER™ + RBV for 16 weeks.
C-SALVAGE (P048)	GT 1 TE with HCV protease inhibitor regimen[‡] with or without cirrhosis	EBR[¶] + GZR[¶] + RBV[†] for 12 weeks (N=79)	Open-label trial in subjects with GT 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with peg-IFN + RBV. Subjects received EBR + GZR RBV for 12 weeks.
C-SWIFT (P074)	GT 1, 3 TN with or without cirrhosis	• ZEPATIER™+ sofosbuvir[§] for 8 or 12 weeks in GT 3 (N= 15 and N=26, respectively) ZEPATIER™+ sofosbuvir[§] for 4, 6 or 8 weeks in GT 1 (N=31, 50, and 21, respectively)	Open-label trial of ZEPATIER™ + sofosbuvir in subjects with GT 1 or 3 infection. Non-cirrhotic GT 3 infected subjects, were randomized (1:1) to 8 or 12 weeks of treatment, and cirrhotic GT 3 infected subjects received 12 weeks of treatment. Non-cirrhotic GT 1 infected subjects, were randomized (1:1) to 4 or 6 weeks of treatment, and cirrhotic GT 1 infected subjects were randomized (1:1) to 6 or 8 weeks of treatment.

GT = Genotype
TN = Treatment-Naïve
TE = Treatment-Experienced (failed prior treatment with interferon [IFN] or peginterferon alfa [peg-IFN] with or without ribavirin (RBV) or were intolerant to prior therapy)
ITG = Immediate Treatment Group
DTG = Delayed Treatment Group
CKD = Chronic Kidney Disease
Pbo = Placebo
[¶] EBR = elbasvir 50 mg; GZR = grazoprevir 100 mg; EBR+GZR = co-administered as single agents
[†]RBV was administered at a total daily dose of 800 mg to 1400 mg based on weight (see **DOSAGE AND ADMINISTRATION**)
[‡] Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with peg-IFN + RBV
[§] Sofosbuvir dose was 400 mg once a day

Sustained virologic response was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR). Serum HCV RNA values were measured during these clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with an LLOQ of 15 HCV RNA IU/mL,

with the exception of C-WORTHY and C-SCAPE where the assay had an LLOQ of 25 HCV RNA IU/mL.

Clinical Trials in Treatment-Naïve Subjects with Genotype 1 and 4 Chronic Hepatitis C Infection

Demographic and baseline characteristics for treatment-naïve subjects with genotype 1, or 4 CHC infection treated with ZEPATIER™ for 12 weeks in C-EDGE TN, C-EDGE COINFECTION, C-SURFER, C-WORTHY, and C-SCAPE are provided in Table 14.

Table 14 -Demographic and Baseline Characteristics of Treatment-Naïve Subjects with or without Cirrhosis Treated with ZEPATIER™ for 12 Weeks

Trial	C-EDGE TN (P060)	C-EDGE COINFECTION (HCV/HIV-1 Co-Infection) (P061)	C-SURFER (CKD Stages 4-5, including hemodialysis) (P052)	C-WORTHY (P035)	C-SCAPE (P047)	All Studies
Regimen	**ZEPATIER™ 12 Weeks N=306 n (%)**	**ZEPATIER™ 12 Weeks N=217 n (%)**	**EBR + GZR 12 Weeks N=101 n (%)**	**EBR + GZR 12 Weeks N=103 n (%)**	**EBR + GZR 12 Weeks N=10 n (%)**	**N=737 n (%)**
Characteristics						
Age (Years)						
Mean (SD)	52 (11)	49 (9)	57 (9)	51 (12)	45 (7)	52 (11)
Gender						
Male	168 (55)	182 (84)	74 (73)	66 (64)	6 (60)	496 (67)
Race						
White	190 (62)	166 (76)	51 (50)	88 (85)	8 (80)	503 (68)
Black or African American	59 (19)	38 (18)	46 (46)	10 (10)	1 (10)	154 (21)
Asian	45 (15)	6 (3)	3 (3)	2 (2)	1 (10)	57 (8)
Other	12 (4)	7 (3)	1 (<1)	3 (3)	0 (0)	23 (3)
IL28B Genotype						
CC	98 (32)	77 (35)	26 (26)	26 (25)	3 (30)	230 (31)
Non-CC	206 (67)	140 (65)	73 (72)	77 (75)	7 (70)	503 (68)
Unknown	2 (<1)	0 (0)	2 (2)	0 (0)	0 (0)	4 (<1)
HCV Genotype						
1a	157 (51)	144 (66)	53 (52)	72 (70)	0 (0)	426 (58)
1b	131 (43)	44 (20)	48 (48)	29 (28)	0 (0)	252 (34)
1-Other	0 (0)	1 (<1)	0 (0)	2 (2)	0 (0)	3 (<1)
4	18 (6)	28 (13)	0 (0)	0 (0)	10 (100)	56 (8)
Baseline HCV RNA						
>800,000 IU/mL	215 (70)	127 (59)	56 (55)	85 (83)	7 (70)	490 (66)
Cirrhosis Status*						
Non-Cirrhotic	236 (77)	182 (84)	97 (96)	74 (72)	10 (100)	599 (81)
Cirrhotic	70 (23)	35 (16)	4 (4)	29 (28)	0 (0)	138 (19)

Hepatic Fibrosis Stage (METAVIR Score)[†*]						
F0 to F2	201(66)	159 (73)	74 (73)	66 (64)	10 (100)	510 (69)
F3	35 (11)	23 (11)	11 (11)	8 (8)	0 (0)	77 (10)
F4	70 (23)	35 (16)	4 (4)	29 (28)	0 (0)	138 (19)
HCV/HIV Co-Infected	0 (0)	217(100)	0 (0)	30 (29)	0 (0)	247 (34)

[†]By liver biopsy or by non-invasive tests.
*12 subjects in C-SURFER with incomplete fibrosis data are counted as non cirrhotic and are not included in hepatic fibrosis stage.

Study results

Table 15 presents treatment outcomes for ZEPATIER™ in treatment-naïve subjects from C-EDGE TN, C-EDGE COINFECTION, C-SURFER, C-WORTHY, and C-SCAPE trials and from the pooled data from these trials. In trials C-EDGE TN and C-SURFER, the treatment outcomes for subjects treated with ZEPATIER™ in the immediate treatment groups and intensive PK arm are presented. In the C-WORTHY and C-SCAPE trials, the addition of RBV to the regimens was not shown to improve the treatment outcomes. Therefore, only the 12 weeks treatment arms without RBV are presented in Table 15.

Table 15 - Treatment Outcomes after 12 Weeks of Treatment in Treatment-Naïve Subjects with or without Cirrhosis

Trial	C-EDGE TN (P060)	C-EDGE COINFECTION (HCV/HIV-1 Co-Infection) (P061)	C-SURFER (CKD Stages 4-5, including hemodialysis) (P052)	C-WORTHY (P035)	C-SCAPE (P047)	All Studies
Regimen	**ZEPATIER™ 12 Weeks N=306**	**ZEPATIER™ 12 Weeks N=217**	**EBR + GZR 12 Weeks N=101**	**EBR + GZR 12 Weeks N=103**	**EBR + GZR 12 Weeks N=(10)**	**N=737**
Overall SVR	95% (291/306)	95% (206/217)	95% (96/101)	94% (97/103)	90% (9/10)	95% (699/737)
95% CI[¶]	(92.0, 97.2)	(91.1, 97.4)	(88.8, 98.4)	(87.7, 97.8)	(55.5, 99.8)	(93.0, 96.3)
Outcome for subjects without SVR						
On-treatment Virologic Failure[#]	<1% (1/306)	0% (0/217)	0% (0/101)	2% (2/103)	0% (0/10)	<1% (3/737)
Relapse	3% (10/306)	3% (7/217)	0% (0/101)	2% (2/103)	0% (0/10)	3% (19/737)
Other[†]	1% (4/306)	2% (4/217)	5% (5/101)	2% (2/103)	10% (1/10)	2% (16/737)
SVR by Genotype						
GT 1a	92% (144/157)	94% (136/144)	98% (52/53)	93% (67/72)	------	94% (399/426)
GT 1b[‡]	98% (129/131)	96% (43/45)	92% (44/48)	97% (30/31)	------	96% (246/255)
GT 4	100% (18/18)	96% (27/28)	------	------	90% (9/10)	96% (54/56)
SVR by Cirrhosis status						
Non-Cirrhotics[§]	94% (223/236)	94% (171/182)	95% (92/97)	93% (69/74)	90% (9/10)	94% (564/599)
Cirrhotics	97% (68/70)	100% (35/35)	100% (4/4)	97% (28/29)	------	98% (135/138)
SVR by HIV status						
HCV mono-infected	95% (291/306)	------	95% (96/101)	97% (71/73)	90% (9/10)	95% (467/490)
HCV/HIV-1 co-infected	------	95% (207/218)	------	87% (26/30)	------	94% (232/247)

[¶]Confidence Interval based on Clopper-Pearson method.
[#]Includes subjects with virologic breakthrough.
[†]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
[‡]Includes genotype 1 subtypes other than 1a or 1b.
[§]Includes 1 subject with cirrhosis status of "unknown" in C-SCAPE.

No HIV-1 infected subjects switched their antiretroviral therapy regimen due to loss of plasma HIV-1 RNA suppression. In treatment-naïve subjects, treatment outcomes were consistent in subjects with or without compensated cirrhosis and in subjects with or without HCV/HIV-1 co-infection. Treatment outcomes were consistent in subjects with or without advanced CKD, including subjects on hemodialysis.

Clinical Trial with 8-Week Treatment in Treatment-Naïve Subjects Without Cirrhosis with Genotype 1b Chronic Hepatitis C Infection

In the C-WORTHY trial, treatment-naïve subjects with genotype 1b CHC without cirrhosis were treated with EBR + GZR with or without RBV for 8 weeks.

Demographic and baseline characteristics for treatment-naïve subjects without cirrhosis and without HIV-1 co-infection, with genotype 1b chronic hepatitis C infection treated with ZEPATIER™ for 8 weeks are provided below.

In the C-WORTHY trial, treatment-naïve subjects with genotype 1b CHC without cirrhosis were treated with EBR + GZR with or without RBV for 8 weeks. In subjects treated with EBR + GZR without RBV, the subjects had a median age of 56 years (range: 28 to 71); 42% of the subjects were male; 81% were White; 19% were Black or African American; 3% were Hispanic or Latino; mean body mass index was 28 kg/m^2; 87% had baseline HCV RNA levels greater than 800,000 IU/mL; 90% had non-C/C IL28B alleles (CT or TT); and 100% had baseline platelets ≥100 10[3]/microL and albumin ≥3.5 gm/dL by liver biopsy or non-invasive tests, all were non-cirrhotic and 94% (29/31) had METAVIR scores of F0-F2 and the other 2 subjects had a METAVIR score of F3.

Study Results

Treatment outcomes in treatment-naïve subjects with genotype 1b without cirrhosis who received EBR + GZR for 8 weeks in C-WORTHY are presented in Table 16. The addition of RBV was not shown to improve the treatment outcomes observed with EBR + GZR.

Table 16 – C-WORTHY: Treatment Outcomes after 8 Weeks of Treatment in Treatment–Naïve Subjects without Cirrhosis with Genotype 1b Chronic Hepatitis C Infection

Trial	**C-WORTHY (P035)**
Regimen	**EBR + GZR 8 Weeks N=31**
Overall SVR	94% (29/31)
95% CI[†]	(78.6, 99.2)
Outcome for subjects without SVR	
On-treatment Virologic Failure	0 (0/31)
Relapse	6% (2/31)
SVR by Hepatic Fibrosis Stage	
Metavir F0 to F2	97% (28/29)
Metavir F3	50% (1/2)
[†]Based on Clopper-Pearson method.	

Clinical Trials in Treatment-Experienced Subjects with Genotype 1, or 4 Chronic Hepatitis C Infection

C-EDGE TE Trial – Treatment-Experienced Subjects who Failed Prior PEG-IFN with RBV Therapy

Demographic and baseline characteristics for treatment-experienced subjects who failed prior PEG-IFN with RBV therapy with genotype 1, or 4 CHC infection are provided in Table 17.

Table 17 - C-EDGE TE: Demographic and Baseline Characteristics for Treatment-Experienced Subjects who Failed Prior Peg-IFN with RBV with or without Cirrhosis

Trial	**C-EDGE TE (P068)**			
Regimen	**ZEPATIER™ 12 weeks N=105 n (%)**	**ZEPATIER™ + RBV 12 weeks N=104 n (%)**	**ZEPATIER™ 16 weeks N=101 n (%)**	**ZEPATIER™ + RBV 16 weeks N=104 n (%)**
Characteristics				
Age (Years)				
Mean (SD)	56 (10)	55 (8)	55 (10)	55 (10)
Gender				
Male	66 (63)	72 (69)	67 (66)	63 (61)
Race				
White	66 (63)	70 (67)	72 (71)	78 (75)
Black or African American	23 (22)	24 (23)	9 (9)	15 (14)
Asian	15 (14)	9 (9)	18 (18)	8 (8)
Other	1 (<1)	1 (<1)	2 (2)	3 (3)
IL28B Genotype				
CC	20 (19)	16 (15)	25 (25)	20 (19)
Non-CC	84 (80)	86 (83)	76 (75)	84 (81)
Missing	1 (<1)	2 (2)	0 (0)	0 (0)
HCV Genotype				
1a	61 (58)	60 (58)	48 (48)	58 (56)
1b	34 (32)	29 (28)	48 (48)	36 (35)
1-Other	1 (<1)	0 (0)	0 (0)	2 (2)
4	9 (9)	15 (14)	5 (5)	8 (8)
Baseline HCV RNA (IU/mL)				
> 800,000 IU/mL	84 (80)	75 (72)	83 (82)	76 (73)
Cirrhosis Status				
Non-Cirrhotic	68 (65)	69 (66)	65 (64)	68 (65)
Cirrhotic	37 (35)	35 (34)	36 (36)	36 (35)
Hepatic Fibrosis Stage(METAVIR Score)[†]				
F0 to F2	49 (47)	55 (53)	53 (52)	55 (53)
F3	19 (18)	14 (13)	12 (12)	13 (12)
F4	37 (35)	35 (34)	36 (36)	36 (35)
HCV/HIV Co-Infected	6 (6)	5 (5)	6 (6)	4 (4)

[†]By liver biopsy or by non-invasive tests.

Study results

Treatment outcomes in subjects treated with ZEPATIER™ with or without RBV for 12 or 16 weeks are presented in Table 18.

Table 18 - C-EDGE TE Trial: Treatment Outcomes after 12 or 16 weeks of Treatment in Treatment-Experienced Subjects who Failed Prior peg-IFN with RBV with or without Cirrhosis

Trial	C-EDGE TE (P068)			
Regimen	**ZEPATIER™ 12 weeks N=105**	**ZEPATIER™ + RBV 12 weeks N=104**	**ZEPATIER™ 16 weeks N=101**	**ZEPATIER™ + RBV 16 weeks N=104**
Overall SVR	92% (97/105)	94% (98/104)	(93% (94/101)	97% (101/104)
95% CI[b]	(85.5, 96.7)	(87.9, 97.9)	(86.2, 97.2)	(91.8, 99.4)
Outcome for subjects without SVR				
On-treatment Virologic Failure[#]	0% (0/105)	0% (0/104)	2% (2/101)	0% (0/104)
Relapse	6% (6/105)	6% (6/104)	4% (4/101)	0% (0/104)
Other[†]	2% (2/105)	0% (0/104)	1% (1/101)	3% (3/104)
SVR by Genotype				
GT 1a	90% (55/61)	93% (56/60)	94% (45/48)	95% (55/58)
GT 1b[‡]	100% (35/35)	97% (28/29)	96% (46/48)	100% (38/38)
GT 4	78% (7/9)	93% (14/15)	60% (3/5)	100% (8/8)
SVR by Cirrhosis status				
Non-Cirrhotics	94% (64/68)	97% (67/69)	92% (60/65)	96% (65/68)
Cirrhotics	89% (33/37)	89% (31/35)	94% (34/36)	100% (36/36)
Response to Prior HCV Therapy				
On-treatment Virologic Failure[¶]	89% (62/70)	91% (60/66)	92% (60/65)	95% (63/66)
Relapser	100% (35/35)	100% (38/38)	94% (34/36)	100% (38/38)
SVR by HIV status				
HCV mono-infected	92% (91/99)	94% (93/99)	94% (89/95)	97% (97/100)
HCV/HIV co-infected	100% (6/6)	100% (5/5)	83% (5/6)	100% (4/4)

[b]Based on Clopper-Pearson method.
[#]Includes subjects with virologic breakthrough or rebound.
[†]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
[‡]Includes genotype 1 subtypes other than 1a or 1b.
[¶]Includes null responders and partial responders

Overall SVR was achieved in 92% and 97% of subjects receiving ZEPATIER™ for 12 weeks and ZEPATIER™ + RBV for 16 weeks, respectively. SVR was 100% in prior relapsers who received ZEPATIER™ for 12 weeks, regardless of genotype or presence of cirrhosis. SVR was 100% in genotype 1b subjects who received ZEPATIER™ for 12 weeks, regardless of the presence of cirrhosis or response to prior HCV therapy.

Among genotype 1a or 4 null or partial responders, the highest response was achieved with the administration of ZEPATIER™ + RBV for 16 weeks. In subjects receiving ZEPATIER™ + RBV for 16 weeks, treatment outcomes were consistent in subjects with or without cirrhosis, and no subject failed due to virologic failure. SVR was achieved in 93% of subjects receiving ZEPATIER™ + RBV for 16 weeks; 90% in subjects receiving ZEPATIER™ alone for 16 weeks; 90% in subjects receiving ZEPATIER™ + RBV for 12 weeks; and 84% in subjects receiving ZEPATIER™ alone for 12 weeks.

No HIV-1 virological failures were observed in subjects who failed prior peg-IFN + RBV with HCV/HIV-1 co-infection. In treatment-experienced subjects, treatment outcomes were consistent in subjects with or without compensated cirrhosis and in subjects with or without HCV/HIV-1 co-infection.

C-SALVAGE Trial – Treatment-Experienced Subjects who Failed Prior PEG-IFN + RBV + HCV Protease Inhibitor Therapy (Boceprevir, Simeprevir, or Telaprevir)

Demographic and baseline characteristics for the C-SALVAGE trial, for subjects who failed prior peg-IFN + RBV with an HCV protease inhibitor with genotype 1 infection with or without cirrhosis treated with GZR + EBR + RBV for 12 weeks are provided in Table19.

Table 19 – C-SALVAGE: Demographic and Baseline Characteristics for Treatment-Experienced Subjects who Failed Prior Peg-IFN + RBV + HCV Protease Inhibitor Therapy (Boceprevir, Simeprevir, or Telaprevir)

Trial	**C-SALVAGE (P048)**
Regimen	**GZR 100 mg + EBR 50 mg + RBV 12 Weeks N=79 n (%)**
Characteristics	
Age (Years)	
Mean (SD)	54 (10)
Gender	
Male	46 (58)
Race	
White	77 (97)
Black Or African American	2 (3)
IL28B Genotype	
CC	2 (3)
Non-CC	77 (97)
HCV Genotype	
1a	30 (38)
1b	49 (62)
Baseline HCV RNA (IU/mL)	
> 800,000 IU/mL	50 (63)
Cirrhosis Status	
Non-Cirrhotic	45 (57)
Cirrhotic	34 (43)
Hepatic Fibrosis Stage (METAVIR Score)[†]	
F0 to F2	37 (47)
F3	8 (10)
F4	34 (43)
Baseline NS3 resistance-associated substitutions	
Absence	43 (54)
Presence	36 (46)
[†]By liver biopsy or by non-invasive tests.	

Study results

Treatment outcome in subjects treated with ZEPATIER™ with ribavirin for 12 weeks are presented in Table 20.

Table 20 – C-SALVAGE: Treatment Outcome in Treatment-Experienced Subjects who Failed Prior Peg-IFN + RBV + HCV Protease Inhibitor Therapy (Boceprevir, Simeprevir, or Telaprevir)

Trial	**C-SALVAGE (P048)**
Regimen	**EBR 50 mg + GZR 100 mg + RBV 12 Weeks N=79**
Overall SVR	96% (76/79)
95% CI[†]	(89.3, 99.2)
Outcome for subjects without SVR	
On-treatment Virologic Failure	0% (0)
Relapse	4% (3/79)
Other[‡]	0% (0)
SVR by Genotype	
1a	93% (28/30)
1b	98% (48/49)
SVR by Cirrhosis status	
Non-Cirrhotics	98% (44/45)
Cirrhotics	94% (32/34)
Baseline NS3 resistance-associated substitutions	
Absence	100% (43/43)
Presence	92% (33/36)

[†]Based on Clopper-Pearson method.
[‡]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Overall SVR was achieved in 96% (76/79) of subjects receiving EBR + GZR + RBV for 12 weeks. Four percent (3/79) of subjects did not achieve SVR due to relapse. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were consistent in subjects with or without NS3 resistance-associated substitutions at baseline (see **MICROBIOLOGY**).

Based on the lack of impact of baseline NS3 resistance-associated substitutions on treatment outcomes, and efficacy analyses among treatment-experienced subjects in the C-SALVAGE and C-EDGE TE trials, the recommended treatment regimen for treatment-experienced patients who have failed peg-IFN + RBV with boceprevir, simeprevir or telaprevir is as follows: for genotype 1 relapsers, administer ZEPATIER™ for 12 weeks; for genotype 1b prior on-treatment virologic failures, administer ZEPATIER™ for 12 weeks; and for genotype 1a, or 4, prior on-treatment virologic failures, administer ZEPATIER™ + RBV for 16 weeks (see **DOSAGE AND ADMINISTRATION**).

Clinical Trial in Subjects with Advanced Chronic Kidney Disease with Genotype 1 Chronic Hepatitis C Infection

Demographic and baseline characteristics for the C-SURFER trial, for subjects with genotype 1 infection, with or without cirrhosis, with advanced chronic kidney disease (CKD) Stage 4 (eGFR 15-29 mL/min/1.73 m^2) or Stage 5 (eGFR < 15 mL/min/1.73 m^2), including subjects on hemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or peg-IFN ± RBV therapy, are provided in Table 21.

Table 21 – C-SURFER: Demographic and Baseline Characteristics in Subjects with Advanced Chronic Kidney Disease who were Treatment-Naïve or had Failed Prior IFN or Peg-IFN ± RBV, with or without Cirrhosis, with Genotype 1 Chronic Hepatitis C Infection

Trial	**C-SURFER (P052)**
Regimen	**EBR + GZR 12 weeks N=122 n (%)**
Characteristics	
Age (Years)	
Mean (SD)	57 (9)
Gender	
Male	92 (75)
Race	
White	61 (50)
Black or African American	55 (45)
Asian	5 (4)
Other	1 (<1)
IL28B Genotype	
CC	32 (26)
Non-CC	88 (72)
Missing	2 (2)
HCV Genotype	
1a	63 (52)
1b	59 (48)
1-Other	0 (0)
Baseline HCV RNA (IU/mL)	
> 800,000 IU/mL	69 (57)
Cirrhosis Status	
Non-Cirrhotic	115 (94)
Cirrhotic	7 (6)
Hepatic Fibrosis Stage (METAVIR Score)[†]	
F0 to F2	87 (71)
F3	13 (11)
F4	7 (6)
No evidence of cirrhosis by biomarker	15 (12)
CKD stages	
Stage 4	22 (18)
Stage 5	100 (82)
Hemodialysis	92 (75)
Prior HCV Treatment Status	
Treatment-naïve	101 (83)
Treatment-experienced	21 (17)

[†]By liver biopsy or by non-invasive tests.

Study results

Treatment outcomes in subjects treated with ZEPATIER™ for 12 weeks in the immediate treatment group and intensive PK arm are presented in Table 22.

Table 22 - C-SURFER Trial: Treatment Outcomes in Subjects with Advanced Chronic Kidney Disease who were Treatment-Naïve or had Failed Prior IFN or Peg-IFN ± RBV, with or without Cirrhosis, with Genotype 1 Chronic Hepatitis C Infection

Trial	**C-SURFER (P052)**
Regimen	**EBR + GZR 12 weeks N=122[¶]**
Overall SVR	94% (115/122)[†]
95% CI[#]	(88.5, 97.7)
Outcome for subjects without SVR	
On-treatment Virologic Failure	0% (0/122)
Relapse	<1% (1/122)
Other[‡]	5% (6/122)
SVR by Genotype	
GT 1a	97% (61/63)
GT 1b[§]	92% (54/59)
SVR by Cirrhosis status	
Non-Cirrhotics	95% (109/115)
Cirrhotics	86% (6/7)
Prior HCV Treatment Status	
Treatment-naïve	95% (96/101)
Treatment-experienced	90% (19/21)
Hemodialysis Status	
No	97% (29/30)
Yes	93% (86/92)
Chronic Kidney Disease Stage	
Stage 4	100% (22/22)
Stage 5	93% (93/100)

[¶]Includes subjects in the intensive PK arm.
[#]Based on Clopper-Pearson method.
[†]SVR was achieved in 99% (115/116) of subjects in the pre-specified primary analysis population, which excluded subjects not receiving at least one dose of study treatment and those with missing data due to death or early study discontinuation for reasons unrelated to treatment response.
[‡]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
[§]Includes genotype 1 subtypes other than 1a or 1b.

Clinical Trial in Treatment-Naïve Subjects with Genotype 3 Chronic Hepatitis C Infection

Demographic and baseline characteristics in the C-SWIFT study, in treatment naïve subjects with genotype 3 CHC with or without cirrhosis, without HIV-1 co-infection, treated with ZEPATIER™ + sofosbuvir for 8 or 12 weeks are provided in Table23.

Table 23 - C-SWIFT Study: Demographic and Baseline Characteristics in Treatment Naïve Subjects, with or without Cirrhosis, with Genotype 3 Chronic Hepatitis C Infection

Trial	**C-SWIFT (P074)**	
Regimen	**ZEPATIER™ + Sofosbuvir 8 weeks N=15 n (%)**	**ZEPATIER™ + Sofosbuvir 12 weeks N=26 n (%)**
Characteristics		
Age (Years)		
Mean (SD)	51 (10)	48 (11)
Gender		
Male	11 (73)	18 (69)
Race		
White	15 (100)	26 (100)
IL28B Genotype		
CC	6 (40)	9 (35)
Non-CC	9 (60)	17 (65)
Baseline HCV RNA		
>800,000 IU/mL	7 (47)	14 (54)
Cirrhosis Status		
Non-Cirrhotic	15 (100)	14 (54)
Cirrhotic	0 (0)	12 (46)
Hepatic Fibrosis Stage (METAVIR Score)[†]		
F0 to F2	14 (93)	11 (42)
F3	1 (7)	3 (12)
F4	0 (0)	12 (46)
[†]By liver biopsy or by non-invasive tests.		

Study results

Treatment outcomes in subjects treated with ZEPATIER™ + sofosbuvir for 8 or 12 weeks are presented in Table 24.

Table 24 - C-SWIFT Study: Treatment Outcomes in Treatment Naïve Subjects, with or without Cirrhosis, with Genotype 3 Chronic Hepatitis C Infection

Trial	C-SWIFT (P074)	
Regimen	**ZEPATIER™ + Sofosbuvir 8 Weeks N=15**	**ZEPATIER™ + Sofosbuvir 12 Weeks N=26**
Overall SVR	93% (14/15)	92% (24/26)
95% CI[‡]	(68.1, 99.8)	(74.9, 99.1)
Outcome for subjects without SVR		
On-treatment Virologic Failure	0% (0/15)	0% (0/26)
Relapse	7% (1/15)	4% (1/26)
Other[†]	0% (0/15)	4% (1/26)
SVR by Cirrhosis status		
Non-Cirrhotics	93% (14/15)	100% (14/14)
Cirrhotics	-----	83% (10/12)

[‡]Based on Clopper-Pearson method.
[†]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Overall SVR was achieved in 92% (24/26) in treatment-naïve subjects with genotype 3 with or without cirrhosis who received EBR + GZR with sofosbuvir for 12 weeks and in 93% (14/15) treatment-naïve subjects without cirrhosis who received EBR + GZR with sofosbuvir for 8 weeks. Based on the overall results, including SVR in patients with cirrhosis, a 12 week regimen of EBR + GZR with sofosbuvir is recommended for treatment-naïve subjects with genotype 3 with or without cirrhosis.

MICROBIOLOGY

Mechanism of Action

ZEPATIER™ combines two direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, grazoprevir inhibited the proteolytic activity of the recombinant NS3/4A protease enzymes from HCV genotypes 1a, 1b, 3, and 4 with IC_{50} values ranging from 4 to 690 pM.

Antiviral Activity

In HCV replicon assays, the EC_{50} values of elbasvir against full-length replicons from genotypes 1a, 1b, 3a, and 4, were 0.004 nM, 0.003 nM, 0.14 nM, and 0.0003 nM, respectively. The median EC_{50} values of elbasvir against chimeric replicons encoding NS5A sequences from clinical isolates were 0.005 nM for genotype 1a (range 0.003-0.009 nM; N=5), 0.009 nM for genotype 1b (range 0.005-0.010 nM; N=5), 0.02 nM for genotype 3a (range 0.01-0.33 nM; N=9), and 0.0007 nM for genotype 4 (range 0.0002-34 nM; N=14).

In HCV replicon assays, the EC_{50} values of grazoprevir against full-length replicons from genotypes 1a, 1b, 3, and 4, were 0.4 nM, 0.5 nM, 35 nM, and 0.3 nM, respectively.

The median EC_{50} values of grazoprevir against chimeric replicons encoding NS3/4A sequences from clinical isolates were 0.8 nM for genotype 1a (range 0.4-5.1 nM; N=10), 0.45 nM for genotype 1b (range 0.2-5.9 nM; N=10), 5.85 nM for genotype 3 (range 2.1-7.6 nM; N=6), and 0.2 nM for genotype 4 (range 0.11-0.33 nM; N=5).

Evaluation of elbasvir in combination with grazoprevir, ribavirin, or sofosbuvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells. Evaluation of elbasvir in combination with ribavirin or sofosbuvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to elbasvir and grazoprevir have been selected in cell culture for genotypes 1a, 1b, 3, and 4 which resulted in the emergence of resistance-associated amino acid substitutions in NS5A or NS3, respectively. The majority of amino acid substitutions in NS5A or NS3 selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterized in genotype 1a, 1b, or 4 replicons. NS5A and NS3 amino acid substitutions were tested in either stable or transient replicon system and in some cases both systems. Maximal reduced antiviral activity is reported.

For elbasvir, in HCV genotype 1a replicons, single NS5A substitutions reduced antiviral activity: Q30D (925-fold), Q30E (56-fold), Q30H (8-fold), Q30R (125-fold), L31I (134-fold), L31M (10-fold), L31V (125-fold), H58D (6-fold), Y93C (50- fold), Y93H (600-fold), Y93N (2000-fold) by 6- to 2000-fold. In genotype 1b replicons, single NS5A substitutions reduced elbasvir antiviral activity: L31F (17-fold), L31M (7-fold), L31V (13-fold) and Y93H (67-fold) by 17- and 67-fold. In genotype 3 replicons, single NS5A substitutions reduced elbasvir antiviral activity: A30D (1280-fold), A30K (50-fold), L31F (143-fold), L31M (330-fold) and Y93H (496-fold) by 50- to 1280-fold. In genotype 4 replicons, single NS5A substitutions reduced antiviral activity: L30H (240-fold), L30F (15-fold), L30S (4-fold), P32L (5-fold), P58D (1828-fold) and Y93H (23-fold) by 4- to 1828-fold. In general, in HCV genotype 1a, 1b, or 4 replicons, combinations of elbasvir resistance-associated substitutions further reduced elbasvir antiviral activity.

For grazoprevir, in HCV genotype 1a replicons, single NS3 substitutions reduced antiviral activity: Y56H (31-fold), A156G (5-fold), D168A (95-fold), D168E (16-fold), D168 F (21-fold)

D168G (32-fold), D168H (12-fold), D168I (40-fold), D168K (212-fold), D168L (11-fold), D168N (8-fold), D168T (98-fold) D168V (56-fold) and D168Y (104-fold) by 5- to 212-fold. V36M, V55A, Q80K/L, and V107I did not impact grazoprevir antiviral activity. In genotype 1b replicons, single NS3 substitutions reduced antiviral activity: Y56H (13-fold), A156T (280-fold), A156V (375-fold), D168A (14-fold), D168F (76-fold), D168G (11-fold), D168H (51-fold), D168I (13-fold), D168K (121-fold), D168L (15-fold), D168T (26-fold), D168V (14-fold), D168Y (8-fold), R155G (28-fold), R155T (13-fold), R155W (27-fold) by 13- to 375-fold. V107I did not impact grazoprevir activity. In genotype 3 replicons, single NS3 substitutions reduced antiviral activity: N77S (7-fold), Q168R (4-fold) and Q178R (5-fold) by 4- to 7-fold. In genotype 4 replicons, single NS3 substitutions reduced antiviral activity: D168A (320-fold) and D168V (110-fold) by 110- to 320-fold. In general, in HCV genotype 1a, 1b, 4, replicons, combinations of grazoprevir resistance-associated substitutions further reduced grazoprevir antiviral activity.

In Clinical Studies

In a pooled analysis of subjects treated with regimens containing elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical trials, resistance analyses were conducted for 50 subjects who experienced virologic failure and had sequence data available (6 with on-treatment virologic failure, 44with post-treatment relapse).

Treatment-emergent substitutions observed in the viral populations of these subjects based on genotypes are shown in Table 25. Treatment-emergent substitutions were detected in both HCV drug targets in 23/37 (62%) genotype 1a, 1/8 (13%) genotype 1b, and 2/5 (40%) genotype 4.

Table 25 - Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of ZEPATIER™ with and without Ribavirin Regimens in Phase 2 and Phase 3 Clinical Trials

Target	Emergent Amino Acid Substitutions	Genotype 1a N = 37 % (n)	Genotype 1b N = 8 % (n)	Genotype 4 N = 5 % (n)
NS3	Any of the following NS3 substitutions: V36L/M, Y56F/H, V107I, R155I/K, A156G/M/T/V, V158A, D168A/C/E/G/N/V/Y, V170I	78% (29)	25% (2)	40% (2)
	V36L/M	11% (4)	--	--
	Y56F/H	14% (5)	13% (1)	--
	V107I	3% (1)	13% (1)	--
	R155I/K	5% (2)	--	--
	A156T	27% (10)	13% (1)	20% (1)
	A156G/V/M	8% (3)	--	60% (3)
	V158A	5% (2)	--	--
	D168A	35% (13)	--	20% (1)
	D168C/E/G/N/V/Y	14% (5)	--	20% (1)
	V170I	--	--	20% (1)
NS5A	Any of the following NS5A substitutions: M/L28A/G/T/S[§] Q30H/K/R/Y, L/M31F/M/I/V, H/P58D, Y93H/N/S	81% (30)	88% (7)	100% (5)
	M/L28A/G/T/S	19% (7)	13% (1)	60% (3)
	Q30H/K/Y	14% (5)	--	--
	Q30R	46% (17)	--	--
	L/M31M/F/I/V[†]	11% (4)	25% (2)	40% (2)
	H/P58D[‡]	5% (3)	--	20% (1)
	Y93H/N/S	14% (5)	63% (5)	20% (1)

[§]Reference sequences for NS5A at amino acid 28 are M (genotype 1a), L (genotype 1b, genotype 4a and 4d).
[†]Reference sequences for NS5A at amino acid 31 are L (genotype 1a and genotype 1b) and M (genotype 4a and 4d).
[‡]Reference sequences for NS5A at amino acid 58 are H (genotype 1a), P (genotype 1b, genotype 4a and 4d).

In an analysis of genotype 3 subjects treated with ZEPATIER™ and sofosbuvir for 12 weeks in a Phase 2 clinical study, one subject experienced relapse. This subject had a treatment-emergent NS5A Y93H substitution.

In Vitro Cross Resistance

Elbasvir is active *in vitro* against genotype 1a NS5A substitutions, M28V and Q30L, genotype 1b substitutions, L28M/V, R30Q, L31V, Y93C, and genotype 4 substitution, M31V which confer resistance to other NS5A inhibitors. In general, other NS5A substitutions conferring resistance to NS5A inhibitors may also confer resistance to elbasvir. NS5A substitutions conferring resistance to elbasvir may reduce the antiviral activity of other NS5A inhibitors. Elbasvir is fully active against substitutions conferring resistance to NS3/4A protease inhibitors: T54S, Q80K, R155K, A156T/V, D168V and D168Y.

Grazoprevir is active *in vitro* against the following genotype 1a NS3 substitutions which confer resistance to other NS3/4A protease inhibitors: V36A/L/M, Q41R, F43L, T54A/S, V55A/I, Y56F, Q80R, V107I, S122A/G/R/T, I132V, A156S, D168S, I170T/V. Grazoprevir is active *in*

vitro against the following genotype 1b NS3 substitutions conferring resistance to other NS3/4A protease inhibitors: V36A/I/L/M, Q41L/R, F43S, T54A/C/G/S, V55A/I, Y56F, Q80L/R, V107I, S122A/G/R, R155E/K/N/Q/S, A156G/S, D168E/N/S, V170A/I/T. Some NS3 substitutions at A156 and at D168 confer reduced antiviral activity to grazoprevir as well as to other NS3/4A protease inhibitors. Grazoprevir is fully active against resistance-associated variants selected by NS5A inhibitors: L31I/M/V and Y93H.

The substitutions associated with resistance to NS5B inhibitors are susceptible to elbasvir or grazoprevir.

Persistence of Resistance-Associated Substitutions

The persistence of elbasvir and grazoprevir treatment-emergent amino acid substitutions in NS5A, and NS3, respectively, was assessed in genotype 1-infected subjects in Phase 2 and 3 trials whose virus had treatment-emergent resistance-associated substitution in the drug target, and with available data through at least 24 weeks post-treatment.

Treatment-emergent NS5A resistance-associated substitutions were generally more persistent than NS3 resistance-associated substitutions. Among genotype 1-infected subjects who had one or more treatment-emergent NS5A resistance-associated substitutions, these substitutions became undetectable at follow-up week 12 in only 5% (2/44) of subjects and 0% (0/12) of subjects with follow-up week 24 data.

Among genotype 1-infected subjects with treatment-emergent NS3 resistance-associated substitutions, these substitutions became undetectable at follow-up week 24 in 67% (10/15) of subjects based on population sequencing.

Due to the limited number of genotype 3- and 4-infected subjects with treatment-emergent NS5A and NS3 resistance-associated substitutions, trends in persistence of treatment-emergent substitutions in these genotypes could not be established.

Effect of Baseline HCV Polymorphisms on Treatment Response

Analyses in Phase 2 and 3 clinical studies of ZEPATIER™, or elbasvir + grazoprevir, with or without ribavirin were conducted to explore the association between baseline NS5A and/or NS3polymorphisms and treatment response among subjects who achieved SVR or experienced virologic failure (see **CLINICAL TRIALS**) and for whom baseline sequences were available. Baseline NS5A polymorphism at position 28, 30, 31, 58, and 93 were evaluated. Baseline NS3 polymorphisms at position 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175 were evaluated. Compared to a reference HCV genotype 1a replicon, the following NS5A substitutions reduced elbasvir antiviral activity by greater than 5-fold: M/L28T/A, Q/R30E/H/R/G/K/L/D, L31M/V/F, H58D, and Y93C/H/N.

Genotype 1a

In pooled analyses of genotype 1a-infected subjects, baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro* were identified in 6% (29/491) of treatment-naïve subjects and 8% (26/334) of treatment-experienced subjects. Among treatment-naïve subjects, SVR was achieved in 98% (432/439) of subjects without baseline

NS5A polymorphisms and 55% (16/29) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.* Among treatment-experienced subjects, SVR was achieved in 99% (291/295) of subjects without baseline NS5A polymorphisms and 50% (13/26) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.*

In pooled analyses, presence of NS3 polymorphisms, including Q80K, prior to the start of therapy did not impact treatment response among genotype 1a-infected subjects.

Genotype 1b

In pooled analyses, presence of NS5A polymorphisms prior to the start of therapy did not impact treatment response among treatment-naïve genotype 1b-infected subjects. NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro* were detected in 14% (36/259) of treatment-experienced subjects. SVR was achieved in 100% (223/223) of subjects without baseline NS5A polymorphisms and 86% (31/36) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.*

In pooled analyses, presence of NS3 polymorphisms prior to the start of therapy did not impact treatment response among genotype 1b-infected subjects.

Genotype 4

In pooled analyses, presence of NS5A polymorphisms prior to the start of therapy did not impact treatment response among genotype 4-infected subjects.

In pooled analyses, presence of NS3 polymorphisms prior to the start of therapy did not impact treatment response among treatment-naïve, genotype 4-infected subjects. Baseline NS3 polymorphisms were identified by population sequencing in 19% (7/36) of treatment-experienced genotype 4-infected subjects. In these subjects, SVR was achieved in 100% (7/7) of subjects with baseline NS3 polymorphisms compared with 86% (25/29) in those without baseline NS3 polymorphism.

Genotype 3

In a Phase 2 study (C-SWIFT) of ZEPATIER™ with sofosbuvir, presence of NS5A polymorphisms prior to the start of therapy did not impact treatment response among genotype 3-infected subjects. Baseline NS5A polymorphisms were identified by population sequencing in 12% (3/25) of treatment-naive genotype 3-infected subjects. In these subjects, SVR was achieved in 100% (3/3) of subjects with baseline NS5A polymorphisms compared with 95% (21/22) in those without baseline NS5A polymorphism.

In this analysis, presence of NS3 polymorphisms prior to the start of therapy did not impact treatment response among treatment-naïve, genotype 3-infected subjects.

No subject had NS5B polymorphisms detected at baseline.

TOXICOLOGY

General Toxicology

Elbasvir

Phospholipidosis in lymphoid organs associated with gastrointestinal tract occurred in dogs and was reversible upon treatment cessation. The No-Observed Adverse Effect Level (NOAEL) was 25 mg/kg/day (approximately 1.6 times the clinical dose based on AUC). The clinical relevance of phospholipidosis is unknown.

No target organ toxicity was identified. The NOAEL in rats, dogs, and mice was the highest dose tested, 1000 mg/kg/day (approximately 9, 7, and 63 times the clinical dose based on AUC, respectively).

Grazoprevir

The target organs identified in the repeat-dose toxicity studies were the hepatobiliary system, the male reproductive organs and the gastrointestinal tract. The safety margin for these changes was >80 times the clinical dose based on AUC.

Mutagenesis and Carcinogenesis

Elbasvir and grazoprevir were not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis, chromosomal aberration in Chinese Hamster Ovary cells, and in *in vivo* rat micronucleus assays.

Carcinogenicity studies with elbasvir or grazoprevir have not been conducted.

If ZEPATIER™ is administered in a regimen containing ribavirin or sofosbuvir, the information for ribavirin or sofosbuvir on carcinogenesis and mutagenesis also applies to this combination regimen (see **product monographs for ribavirin or sofosbuvi**r).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

ZEPATIER™
50 mg of elbasvir and 100 mg of grazoprevir

Read this carefully before you start taking **ZEPATIER™** and each time you get a refill. Some of the information may have changed. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ZEPATIER™**.

Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

Your doctor might also want you to take ZEPATIER™ with ribavirin or sofosbuvir. It is very important that you also read the patient product information for these other medicines if you are taking either or them with ZEPATIER™.

If you have any questions about your medicines, please ask your doctor or pharmacist.

What is ZEPATIER™ used for?
ZEPATIER™ is used for the treatment of chronic (lasting a long time) hepatitis C virus genotypes 1, 3, and 4 infection in adults 18 years of age and older. Your treatment regimen will depend on the type of hepatitis C virus you have, whether or not you have cirrhosis (liver scarring) and your treatment history. Your doctor will decide if this drug is right for you.

How does ZEPATIER™ work?
Patients with hepatitis C infection have the virus in their blood and in their liver.

ZEPATIER™ blocks two different proteins from the virus that are needed to make new viruses, and this helps to clear the virus from the body in most people.

What are the ingredients in ZEPATIER™?
Medicinal ingredients: elbasvir and grazoprevir

Non-medicinal ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, sodium chloride, sodium lauryl sulfate, vitamin E polyethylene glycol succinate.

The tablets are film-coated with a coating material containing the following inactive ingredients: carnauba wax, ferrosoferric oxide, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide and triacetin.

ZEPATIER™ comes in the following dosage form:
ZEPATIER™ (elbasvir 50 mg and grazoprevir 100 mg)
The film-coated tablets are beige oval-shaped with the number 770 on it.

Do not use ZEPATIER™ if:
- are allergic to elbasvir, grazoprevir or any of the other ingredients of ZEPATIER™. See **What are the ingredients in ZEPATIER™?** for a complete list of ingredients.
- have moderate or severe liver problems.
- you are taking any of the following medicines:
  - rifampin for tuberculosis
  - HIV protease inhibitors such as atazanavir, darunavir, lopinavir, saquinavir, or tipranavir
  - efavirenz (Sustiva*) or etravirine (Intelence*) for HIV
  - cyclosporine to stop organ transplant rejection
  - carbamazepine (Tegretol*) or phenytoin (Dilantin*): medicines for epilepsy and seizures
  - St. John's wort (Hypericum perforatum, a herbal medicine) for depression or other problems.

If you are using ZEPATIER™ with ribavirin or sosfosbuvir, read the patient information for the other products for further directions when not to use these medications.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZEPATIER™. Talk about any health conditions or problems you may have, including if you:
- have liver problems other than hepatitis C infection.
- have ever taken any medicine for hepatitis C.
- have any other medical conditions.
- are pregnant, or plan to become pregnant, breastfeed or plan to breastfeed.

Tell your doctor right away if you develop the following symptoms of liver problems such as:
- loss of appetite.
- nausea and vomiting.
- feeling tired and weak.
- abdominal pain.
- yellowing of your skin or eyes.
- colour changes in your stool.

Your doctor will decide if ZEPATIER™ is right for you.

Other warnings you should know about:

Pregnancy
- Tell your doctor if you are pregnant or plan to become pregnant.
- We don't know if ZEPATIER™ will harm your baby while you are pregnant.

If you're taking both ZEPATIER™ and ribavirin

- **If you or your partner are pregnant or plan to become pregnant, do not take ribavirin.** Avoid pregnancy while you are taking ZEPATIER™ with ribavirin and for 6 months after stopping ribavirin.
- Read the ribavirin package leaflet for important information on how it can affect pregnancy.
- If you (or your partner) do become pregnant while taking ribavirin or within 6 months after you stop taking ribavirin, tell your doctor right away.

Breast-feeding

- Tell your doctor if you are breastfeeding or planning to breastfeed.
- We don't know if ZEPATIER™ gets in your breast milk and gets passed to your baby.
- It is recommended that you do not breastfeed while taking ZEPATIER™.

Tell your healthcare professional about all the medicines you take, including any prescription and non-prescription drugs, vitamins, minerals, natural and herbal supplements or alternative medicines.

ZEPATIER™ and other medicines may affect each other.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

The following medicines may interact with ZEPATIER™:

Do not take ZEPATIER™ and tell your doctor if you are taking any of the following medicines:

- bosentan (Tracleer*): for pulmonary arterial hypertension
- modafinil (Alertec*): to help people who cannot stay awake

Tell your doctor or pharmacist if you are taking any of the following medicines:

- ketoconazole: to treat fungal infections
- tacrolimus: to stop organ transplant rejection
- elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate: a drug combination to treat HIV

Tell your doctor or pharmacist if you take any of the following medicines for lowering blood cholesterol:

- atorvastatin (Lipitor*)
- fluvastatin (Lescol*)
- rosuvastatin (Crestor*)
- simvastatin(ZOCOR®)

- lovastatin

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking ZEPATIER™.

How to take ZEPATIER™:
Take ZEPATIER™ exactly as your doctor tells you to take it.
- ZEPATIER™ comes in a blister pack of individually-packaged pills. Be sure to keep the pills in this pack until you are ready to take your medicine.
- You can take ZEPATIER™ with or without food.
- Do not stop taking ZEPATIER™ without first talking with your doctor.

Usual adult dose:
Take one tablet a day at the same time every day. Your doctor will tell you for how many weeks you should take ZEPATIER™.

Overdose:

If you think you have taken too much of ZEPATIER™, contact your healthcare professional or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
It is important not to miss a dose of this medicine. If you do miss a dose, work out how long it is since you should have taken ZEPATIER™:
- If it has been less than 16 hours since you should have taken your dose, take the missed dose as soon as possible. Then take your next dose at your usual time.
- If it has been more than 16 hours since you should have taken your dose, do not take the missed dose. Wait and take the next dose at your usual time.
- Do not take a double dose (two doses together) to make up for a forgotten dose.

What are possible side effects from using ZEPATIER™?

These are not all the possible side effects you may feel when taking ZEPATIER™. If you experience any side effects not listed here, contact your healthcare professional. Please also see **Other warnings you should know about**.

Very common side effects of ZEPATIER™ (more than 10%):
- headache.
- feeling tired.

Common side effects of ZEPATIER™ (1-10%):

- abdominal pain.
- constipation.
- diarrhea.
- dry mouth.
- vomiting.
- nausea.
- weakness.
- decreased appetite.
- joint pain.
- muscle pain.
- dizziness.
- anxiety.
- difficulty sleeping.
- irritability.
- hair loss.
- itching.

Common and very common side effects of ZEPATIER™ when used with ribavirin:

- headache.
- feeling tired or weak.
- nausea or vomiting.
- itching.
- muscle aches.
- rash.
- trouble sleeping.
- low red blood cell counts.
- trouble breathing.
- indigestion.
- feeling less hungry.
- cough.
- feeling irritable.

Common side effects of ZEPATIER™ when used with sofosbuvir:

- headache.
- nausea.
- diarrhea.
- feeling tired.

Your doctor will do blood tests to check how your liver is working before and while you are taking ZEPATIER™.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep ZEPATIER™ in its original blister pack until you are ready to take it. Do not take the pills out of the original blister pack to store in another container such as a pill box. This is important because the pills are sensitive to moisture. The pack is designed to protect them.
- Keep ZEPATIER™ at room temperature (15°C - 30°C). Protect from moisture.

Keep out of reach and sight of children.

If you want more information about ZEPATIER™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or Merck Canada website www.merck.ca or by calling Merck Canada at 1-800-567-2594.

To report an adverse event related to ZEPATIER™, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

Last Revised: January 19, 2016

THE ATTACHED IS EXHIBIT "H" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 13TH DAY OF OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

Product Monograph

INCLUDING PATIENT MEDICATION INFORMATION

Pr EPCLUSA™

(sofosbuvir/velpatasvir) Tablets

400 mg/100 mg

Antiviral Agent

Gilead Sciences Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3
Canada

www.gilead.ca

Date of Preparation:
July 8, 2016

Submission Control No.: 190521

TABLE OF CONTENTS

EPCLUSA™
sofosbuvir/velpatasvir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 400 mg sofosbuvir/100 mg velpatasvir	Not applicable

*For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

EPCLUSA (sofosbuvir/velpatasvir) is indicated:

- for the treatment of chronic hepatitis C virus (HCV) infection in adults without cirrhosis or with compensated cirrhosis
- in combination with ribavirin for the treatment of chronic hepatitis C virus (HCV) infection in adults with decompensated cirrhosis.

Geriatrics (≥ 65 years of age)

The response rates observed for patients 65 years of age and over were similar to those of younger patients across treatment groups. EPCLUSA can be administered in geriatric patients (see **ACTION AND CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS**).

Pediatrics (< 18 years of age)

Safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

EPCLUSA is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

When EPCLUSA is used in combination with ribavirin, the contraindications to ribavirin are also applicable to the combination regimen. Refer to the Product Monograph containing information on ribavirin for a list of contraindications for ribavirin.

WARNINGS AND PRECAUTIONS

General

Treatment with EPCLUSA should be initiated and monitored by a physician experienced in the management of chronic hepatitis C virus (HCV) infection.

Data to support the treatment of patients with decompensated cirrhosis who are infected with HCV genotype 2 or genotype 4 are limited, and there are no data for genotype 5 and genotype 6 HCV infected patients with decompensated cirrhosis. The indication for treatment of these patients is based on extrapolation of relevant clinical and *in vitro* data (see **CLINICAL TRIALS** and **MICROBIOLOGY**).

EPCLUSA should not be administered concurrently with other medicinal products containing sofosbuvir.

Use with Potent P-gp Inducers and/or Moderate to Potent Inducers of CYP

Medicinal products that are potent P-glycoprotein (P-gp) inducers and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 [e.g. rifampin, St. John's wort (*Hypericum perforatum*) and carbamazepine] may significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir leading to reduced therapeutic effect of EPCLUSA and potential loss of virologic response. These agents should not be used with EPCLUSA (see **DRUG INTERACTIONS**).

Cardiovascular

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with daclatasvir or simeprevir. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen (HARVONI® [ledipasvir/sofosbuvir]). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with EPCLUSA is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered EPCLUSA:

- Counsel patients about the risk of symptomatic bradycardia.

- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking EPCLUSA who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting EPCLUSA should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

Hepatic

The safety and efficacy of EPCLUSA has not been established in patients with severe hepatic impairment (Child-Pugh Class C) (see **ACTION AND CLINICAL PHARMACOLOGY**).

Monitoring of liver function including direct bilirubin is recommended in patients with decompensated cirrhosis.

Renal

The safety and efficacy of EPCLUSA has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY)**.

Resistance

The efficacy of EPCLUSA has not been established in patients who have previously failed treatment with other regimens that include a NS5A inhibitor (see **MICROBIOLOGY, Cross Resistance**).

Sexual Function/Reproduction

There are no data on the effect of sofosbuvir and velpatasvir on human fertility. No effects on fertility were observed in animal studies for sofosbuvir and velpatasvir (see **TOXICOLOGY**).

Special Populations

Pregnant Women

Use without Ribavirin

Pregnancy should be avoided while taking EPCLUSA as there are no data on the use of EPCLUSA in pregnant women. EPCLUSA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their health care provider immediately in the event of a pregnancy.

No effects on pre- or post-natal development were observed in animal reproduction studies at the highest doses of sofosbuvir tested. In the rat and rabbit embryo fetal studies, and the rat pre/post-natal study, exposure to the predominant circulating metabolite GS-331007 at the highest dose was approximately 5-fold, 14-fold, and 6-fold the exposure in humans at the recommended clinical dose, respectively.

No effects on pre- or post-natal development have been observed in animal reproduction studies at the highest doses of velpatasvir tested. In the mouse, rat, and rabbit embryo fetal studies, and rat pre/post-natal study velpatasvir exposure was approximately 31-fold, 6-fold, 0.7-fold, and 5-fold the exposure in humans at the recommended clinical dose, respectively.

Use with Ribavirin

If EPCLUSA is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Women of childbearing potential and their male partners must use two forms of effective contraception during treatment and for 6 months after the treatment has concluded. Routine monthly pregnancy tests must be performed during this time. Refer to the ribavirin Product Monograph for a full list of warnings and precautions for ribavirin.

Nursing Women

It is not known whether sofosbuvir, velpatasvir, or their metabolites are excreted in human breast milk. The sofosbuvir predominant circulating metabolite GS-331007, and velpatasvir, are present in the milk of lactating rats; they had no clear effect on nursing pups. Because a risk to the newborn/infant cannot be excluded, mothers should be instructed not to breastfeed if they are taking EPCLUSA.

Pediatrics (< 18 years of age)

The safety and efficacy of EPCLUSA in pediatric patients have not been established.

Geriatrics (≥ 65 years of age)

The response rates observed for patients 65 years of age and over were similar to those of patients < 65 years of age across treatment groups.

Liver Transplant Patients

The safety and efficacy of EPCLUSA has not been established in patients with recurrent HCV infection after liver transplant.

HCV/HIV Co-infection

The safety and efficacy of EPCLUSA has not been established in HCV patients co-infected with Human Immunodeficiency Virus (HIV).

EPCLUSA has been shown to increase tenofovir exposure when used together with an HIV regimen containing tenofovir disoproxil fumarate (tenofovir DF). Patients receiving EPCLUSA concomitantly with tenofovir DF, particularly those at increased risk for renal dysfunction, should be monitored for tenofovir-associated adverse reactions. Refer to Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.

Efavirenz has been shown to significantly decrease the concentration of velpatasvir; therefore co-administration of EPCLUSA with an efavirenz-containing regimen is not recommended (see **DRUG INTERACTIONS**).

HCV/HBV Co-infection

EPCLUSA is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of EPCLUSA have not been established in HCV patients co-infected with HBV.

Monitoring and Laboratory Tests

If EPCLUSA is administered with amiodarone, close monitoring for bradycardia is recommended. Refer to the amiodarone Product Monograph (see **WARNINGS AND PRECAUTIONS**, **Drug Interactions**).

Monitoring of liver function including direct bilirubin is recommended in patients with decompensated cirrhosis (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety profile of EPCLUSA was established in non-cirrhotic and cirrhotic (compensated and decompensated) patients infected with HCV.

The safety assessment of EPCLUSA was based on pooled Phase 3 clinical trial data (ASTRAL-1, ASTRAL-2, and ASTRAL-3) from patients with HCV without cirrhosis or with compensated cirrhosis including 1035 patients who received EPCLUSA for 12 weeks. The proportion of patients who permanently discontinued treatment due to adverse events was 0.2% for patients receiving EPCLUSA for 12 weeks. Of the 1035 patients, 2% had at least one serious adverse

event (SAE), with no patients experiencing a treatment-related SAE.

The safety of EPCLUSA was also assessed in patients with decompensated cirrhosis (Child-Pugh B) in one Phase 3 trial (ASTRAL-4). In ASTRAL-4, the proportion of patients who permanently discontinued treatment due to adverse events was 5% (4/87) for those patients treated with EPCLUSA + RBV for 12 weeks, 1% (1/90) for those patients treated with EPCLUSA for 12 weeks, and 4% (4/90) for those patients treated with EPCLUSA for 24 weeks. Serious adverse events occurred in 19% (17/90), 16% (14/87) and 18% (16/90) of patients treated with EPCLUSA for 12 weeks, EPCLUSA + RBV for 12 weeks and EPCLUSA for 24 weeks, respectively. One patient (0.4%) experienced SAEs considered related to EPCLUSA.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Patients with Compensated Liver Disease:

The adverse reactions (Grades 2 to 4) observed in ≥ 2% of patients receiving 12 weeks of treatment with EPCLUSA in clinical trials are listed in Table 1.

Table 1. Adverse Reactions (Grades 2-4) Reported in ≥ 2% of Patients Receiving 12 Weeks of EPCLUSA[a] from the Pooled Phase 3 Studies (ASTRAL-1, ASTRAL-2, ASTRAL-3)

	EPCLUSA 12 weeks	Placebo 12 weeks
	N = 1035	N = 116
Headache	4%	3%
Fatigue	3%	1%

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Adverse reactions (Grades 2 to 4) occurring in less than 2% of patients receiving 12 weeks of treatment with EPCLUSA in clinical trials are listed below by body system:

Table 2. Adverse Reactions (Grades 2-4) Reported in < 2% of Patients Receiving 12 Weeks of EPCLUSA[a] from the Pooled Phase 3 Studies (ASTRAL-1, ASTRAL-2, ASTRAL-3)

Body System	EPCLUSA 12 Weeks
Blood And Lymphatic System Disorders	Leukopenia
Cardiac Disorders	Palpitations
Ear and labyrinth disorders	Vertigo
Gastrointestinal Disorders	Abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhea, dry mouth, dyspepsia, flatulence, gastroesophageal reflux disease, nausea, stomatitis, tongue coated, toothache, vomiting
General Disorders And Administration Site Conditions	Asthenia, chest pain, edema peripheral, influenza like illness, pain, pyrexia
Infections And Infestations	Lower respiratory tract infection, nasopharyngitis, sinusitis
Investigations	Electrocardiogram QT prolonged, weight decreased
Metabolism and Nutrition Disorders	Decreased appetite, gout, increased appetite
Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle spasms, musculoskeletal pain, myalgia, neck pain, osteoarthritis, pain in extremity, spinal pain, tendon pain
Nervous System Disorders	Disturbance in attention, dizziness, dysgeusia, migraine, psychomotor hyperactivity, somnolence
Psychiatric Disorders	Anxiety, apathy, attention deficit/hyperactivity disorder, confusional state, depressed mood, depression, insomnia, irritability, loss of libido, mood swings, sleep disorder
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnoea, epistaxis, oropharyngeal pain
Skin And Subcutaneous Tissue Disorders	Alopecia, eczema, pruritus, pruritus generalised, rash, rash pruritic
Vascular Disorders	Hypertension, hypertensive crisis, hypotension

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Abnormal Hematologic and Clinical Chemistry Findings

The frequency of treatment-emergent laboratory abnormalities (Grades 2-4) occurring in at least 2% of patients receiving 12 weeks of treatment with EPCLUSA are described in Table 3.

Table 3. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 2% of Patients Receiving 12 Weeks of EPCLUSA from the Pooled Phase 3 Studies (ASTRAL-1, ASTRAL-2, ASTRAL-3)

Laboratory Abnormality Parameters	EPCLUSA 12 weeks N = 1035	Placebo 12 weeks N = 116
Chemistry		
Hyperglycemia (> 8.91 mmol/L)	11%	12%
Hypoglycemia (< 3.03 mmol/L)	2%	< 1%
Lipase (> 1.5 x ULN)	8%	4%
Hematology		
Platelets (< 100 x 10^9/L)	2%	4%

ULN = Upper Limit of Normal

Patients With Decompensated Cirrhosis:

The adverse reactions (Grades 2 to 4) observed in ≥ 2% of patients receiving 12 or 24 weeks of treatment with EPCLUSA or 12 weeks of treatment with EPCLUSA plus ribavirin in the ASTRAL-4 study are listed in Table 4.

Table 4. Adverse Reactions (Grades 2-4) Reported in ≥ 2% of Patients Receiving 12 or 24 Weeks of EPCLUSA[a] without Ribavirin or 12 Weeks of EPCLUSA with Ribavirin in ASTRAL-4

	EPCLUSA 12 weeks N = 90	EPCLUSA + RBV 12 weeks N = 87	EPCLUSA 24 weeks N = 90
Anemia	0	14%	0
Decreased appetite	0	0	3%
Diarrhea	0	2%	0
Dyspnea	0	3%	0
Fatigue	2%	8%	3%
Headache	7%	1%	1%
Insomnia	0	2%	1%
Rash	1%	2%	0

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Adverse reactions (Grades 2 to 4) occurring in less than 2% of patients receiving 12 or 24 weeks of EPCLUSA or 12 weeks of EPCLUSA with ribavirin in ASTRAL-4 are listed below by body system:

Table 5. Adverse Reactions (Grades 2-4) Reported in < 2% of Patients Receiving 12 or 24 Weeks of EPCLUSA[a] or 12 Weeks of EPCLUSA with Ribavirin from ASTRAL-4

Body System	EPCLUSA 12 Weeks	EPCLUSA + RBV 12 Weeks	EPCLUSA 24 Weeks
Cardiac Disorders	N/A	Palpitations	N/A
Gastrointestinal Disorders	Vomiting	Vomiting	Abdominal discomfort, abdominal pain upper, gastroesophageal reflux disease
General Disorders And Administration Site Conditions	N/A	Asthenia	N/A
Hepatobiliary Disorders	N/A	N/A	Hepatorenal syndrome
Infections And Infestations	N/A	N/A	Peritonitis, sepsis
Investigations	N/A	N/A	Weight decreased
Metabolism and Nutrition Disorders	N/A	N/A	Diabetes mellitus
Musculoskeletal and Connective Tissue Disorders	Arthralgia	N/A	N/A
Nervous System Disorders	N/A	Headache, tremor	Headache, poor quality sleep
Psychiatric Disorders	Anxiety, depression	N/A	Anxiety, insomnia
Respiratory, Thoracic and Mediastinal Disorders	N/A	Dyspnea exertional	N/A
Skin And Subcutaneous Tissue Disorders	Rash	Pruritus, rash pruritic	Dermatitis contact
Vascular Disorders	N/A	Hypertension	Hypotension

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

N/A: Not applicable

Abnormal Hematologic and Clinical Chemistry Findings

The frequency of treatment-emergent laboratory abnormalities (Grades 2-4) occurring in at least 2% of patients receiving 12 or 24 weeks of treatment with EPCLUSA or 12 weeks of treatment with EPCLUSA + RBV are described in Table 6 below

Table 6. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 2% of Patients Receiving 12 or 24 Weeks of EPCLUSA or 12 Weeks of EPCLUSA with Ribavirin from ASTRAL-4

Laboratory Abnormality Parameters	EPCLUSA 12 Weeks	EPCLUSA + RBV 12 Weeks	EPCLUSA 24 Weeks
	N = 90	N = 87	N = 90
Chemistry			
Albumin (< 30 g/L)	14%	13%	17%
Alkaline phosphatase (> 2.5 x ULN)	2%	1%	0
Amylase (> 1.5 x ULN)	4%	6%	10%
AST (> 2.5 x ULN)	2%	1%	4%
Creatine kinase (≥ 6 x ULN)	4%	2%	3%
GGT (> 2.5 x ULN)	3%	0	3%
Hyperbilirubinemia (> 1.5 x ULN)	18%	54%	13%
Hyperglycemia (> 8.91 mmol/L)	42%	47%	47%
Hypokalemia (< 3.0 mmol/L)	2%	2%	1%
Hypoglycemia (< 3.03 mmol/L)	3%	0	7%
Hyponatremia (< 130 mmol/L)	8%	8%	9%
Lipase (> 1.5 x ULN)	29%	29%	30%
Hematology			
Hemoglobin (< 100 g/L)	9%	24%	11%
INR (> 1.5 x ULN)	1%	0	2%
Lymphocytes (< 0.6 x 10^9/L)	20%	38%	23%
Neutrophils (< 1.0 x 10^9/L)	3%	5%	9%
Platelets (< 100 x 10^9/L)	27%	31%	37%
White Blood Cells (< 2.0 x 10^9/L)	4%	13%	7%

ULN = Upper Limit of Normal

Among patients with decompensated cirrhosis in the ASTRAL-4 trial, direct bilirubin was found to remain stable (< 17.1 µmol/L change from baseline throughout treatment) in the majority of patients. One patient randomized to receive 24 weeks of treatment with EPCLUSA had a > 17.1 µmol/L increase from baseline in direct bilirubin from Week 6 through Week 10 for which no clinical explanation could be identified; this patient completed 24 weeks of treatment.

Post-Market Adverse Drug Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions have been identified during post approval use of sofosbuvir. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Serious symptomatic bradycardia when amiodarone is coadministered with sofosbuvir in combination with another HCV direct acting antiviral (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **DRUG INTERACTIONS**).

DRUG INTERACTIONS

Overview

As EPCLUSA contains sofosbuvir and velpatasvir, any interactions that have been identified with these agents individually may occur with EPCLUSA.

After oral administration of EPCLUSA, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. In clinical pharmacology studies, both sofosbuvir and the primary circulating metabolite GS-331007 (dephosphorylated nucleotide metabolite) were monitored for purposes of pharmacokinetic analyses.

Drug-Drug Interactions

Potential for EPCLUSA to Affect Other Drugs

Velpatasvir is an inhibitor of drug transporter P-gp, breast cancer resistance protein (BCRP), OATP1B1 and OATP1B3. Coadministration of EPCLUSA with drugs that are substrates of these transporters may increase the exposure of such drugs. The drug-drug interaction potential of velpatasvir is limited to the presystemic processes (intestinal efflux and hepatic uptake); clinically relevant interactions in systemic circulation are not expected.

At clinically relevant concentration, velpatasvir is not an inhibitor of hepatic transporters OATP1A2 or OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

Sofosbuvir and GS-331007 are not relevant inhibitors of efflux drug transporters P-gp, BCRP, renal efflux transporter MRP2, hepatic efflux transporter BSEP, hepatic uptake transporters OATP1B1, OATP1B3, OCT1, and GS-331007 is not an inhibitor of renal uptake transporters OAT1, OCT2 and renal efflux transporter MATE1. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Potential for Other Drugs to Affect EPCLUSA

Sofosbuvir and velpatasvir are substrates of efflux drug transporters P-gp and BCRP while GS-331007 is not. GS-331007 is not a substrate for renal transporters including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2. Velpatasvir is poorly transported by OATP1B1 and OATP1B3. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

Drugs that are P-gp inducers and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. rifampin, St. John's wort or carbamazepine) may significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir leading to reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended (see **WARNINGS AND PRECAUTIONS**).

Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir and/or velpatasvir plasma concentrations without increasing GS-331007 plasma concentration. Drugs that inhibit CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir. EPCLUSA may be coadministered with P-gp, BCRP, and CYP inhibitors.

Table 7 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either EPCLUSA, the components of EPCLUSA (sofosbuvir and velpatasvir) as individual agents, or are predicted drug interactions that may occur with EPCLUSA. The table is not all-inclusive (see **ACTION AND CLINICAL PHARMACOLOGY**).

Table 7. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid Reducing Agents:	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g. aluminum and magnesium hydroxide)		It is recommended to separate antacid and EPCLUSA administration by 4 hours.
H_2-receptor antagonists[c] (e.g. famotidine)		H_2-receptor antagonists may be administered simultaneously with or staggered from EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g. omeprazole)		Proton-pump inhibitor doses comparable with omeprazole 20 mg or lower can be administered with EPCLUSA when EPCLUSA is administered with food.
Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir and velpatasvir concentrations unknown	Coadministration of amiodarone with EPCLUSA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with EPCLUSA is not recommended; if coadministration is required, cardiac monitoring is recommended (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).
digoxin[c]	↑ digoxin	Coadministration of EPCLUSA with digoxin may increase the concentration of digoxin due to intestinal inhibition of P-gp by velpatasvir. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with EPCLUSA.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir	Coadministration of EPCLUSA with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of EPCLUSA. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[c] rifapentine*	↓ sofosbuvir ↓ velpatasvir	Coadministration of EPCLUSA with rifabutin, rifampin, or rifapentine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of EPCLUSA. Coadministration is not recommended.
Antiretrovirals: efavirenz[c]	↓ velpatasvir	Coadministration of EPCLUSA with efavirenz is expected to decrease the concentration of velpatasvir. Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Regimens containing tenofovir disoproxil fumarate[c] (tenofovir DF)	↑ tenofovir	EPCLUSA has been shown to increase tenofovir exposure. Patients receiving tenofovir DF and EPCLUSA concomitantly should be monitored for adverse reactions associated with tenofovir DF. Refer to the Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.
HMG-CoA Reductase Inhibitors rosuvastatin[c]	↑ rosuvastatin	Coadministration of EPCLUSA with rosuvastatin may increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg.

*Drug not marketed in Canada

a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease.
c These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with EPCLUSA

Based on drug interaction studies conducted with the components of EPCLUSA (sofosbuvir or velpatasvir) or EPCLUSA, no clinically significant drug interactions have been either observed or are expected when EPCLUSA is used with the following drugs: atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, ketoconazole, lopinavir/ritonavir, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, or tacrolimus (see **DRUG INTERACTIONS**, **Assessment of Drug Interactions**).

Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of sofosbuvir, GS-331007 and velpatasvir are shown in Table 8. The effects of sofosbuvir, velpatasvir or EPCLUSA on the exposure of coadministered drugs are shown in Table 9.

Table 8. Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir and the Predominant Circulating Metabolite GS-331007, and Velpatasvir in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofos-buvir Dose (mg)	Velpa-tasvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007 and Velpatasvir PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Antibiotic								
Rifampin[f]	600 once daily	400 single dose	ND	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
					GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA
		ND	100 single dose	12	velpatasvir	0.29 (0.23, 0.37)	0.18 (0.15, 0.22)	NA
	600 single dose	ND	100 single dose	12	velpatasvir	1.28 (1.05, 1.56)	1.46 (1.17, 1.83)	NA
Anti-HIV Drugs								
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF	300/100 + 200/300 once daily	400 once daily	100 once daily	24	sofosbuvir	1.12 (0.97, 1.29)	1.22 (1.12, 1.33)	NA
					GS-331007	1.21 (1.12, 1.29)	1.32 (1.27, 1.36)	1.42 (1.37, 1.49)
					velpatasvir	1.55 (1.41, 1.71)	2.42 (2.23, 2.64)	4.01 (3.57, 4.50)
Darunavir/ ritonavir + emtricitabine/ tenofovir DF	800/100 + 200/300 once daily	400 once daily	100 once daily	29	sofosbuvir	0.62 (0.54, 0.71)	0.72 (0.66, 0.80)	NA
					GS-331007	1.04 (0.99, 1.08)	1.13 (1.08, 1.18)	1.13 (1.06, 1.19)
					velpatasvir	0.76 (0.65, 0.89)	0.84 (0.72, 0.98)	1.01 (0.87, 1.18)
Dolutegravir	50 once daily	400 once daily	100 once daily	24	sofosbuvir	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA
					GS-331007	1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
					velpatasvir	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)
Efavirenz/ emtricitabine/ tenofovir DF[b]	600/200/300 once daily	400 once daily	100 once daily	14	sofosbuvir	1.38 (1.14, 1.67)	0.97 (0.83, 1.14)	NA
					GS-331007	0.86 (0.80, 0.93)	0.90 (0.85, 0.96)	1.01 (0.95, 1.07)
					velpatasvir	0.53 (0.43, 0.64)	0.47 (0.39, 0.57)	0.43 (0.36, 0.52)

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	Velpatasvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007 and Velpatasvir PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide[c]	150/150/200/10 once daily	400 once daily	100 once daily	23	sofosbuvir	1.23 (1.07, 1.42)	1.37 (1.24, 1.52)	NA
					GS-331007	1.29 (1.25, 1.33)	1.48 (1.43, 1.53)	1.58 (1.52, 1.65)
					velpatasvir	1.30 (1.17, 1.45)	1.50 (1.35, 1.66)	1.60 (1.44, 1.78)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir DF[d]	150/150/200/ 300 once daily	400 once daily	100 once daily	24	sofosbuvir	1.01 (0.85, 1.19)	1.24 (1.13, 1.37)	NA
					GS-331007	1.13 (1.07, 1.18)	1.35 (1.30, 1.40)	1.45 (1.38, 1.52)
					velpatasvir	1.05 (0.93, 1.19)	1.19 (1.07, 1.34)	1.37 (1.22, 1.54)
Emtricitabine/ rilpivirine/ tenofovir DF[e]	200/25/300 once daily	400 once daily	100 once daily	24	sofosbuvir	1.09 (0.95, 1.25)	1.16 (1.09, 1.24)	NA
					GS-331007	0.96 (0.90, 1.01)	1.04 (1.00, 1.07)	1.12 (1.07, 1.17)
					velpatasvir	0.96 (0.85, 1.10)	0.99 (0.88, 1.11)	1.02 (0.91, 1.15)
Lopinavir/ ritonavir + emtricitabine/ tenofovir DF	4 x 200/50 + 200/300 once daily	400 once daily	100 once daily	24	sofosbuvir	0.59 (0.49, 0.71)	0.71 (0.64, 0.78)	NA
					GS-331007	1.01 (0.98, 1.05)	1.15 (1.09, 1.21)	1.15 (1.07, 1.25)
					velpatasvir	0.70 (0.59, 0.83)	1.02 (0.89, 1.17)	1.63 (1.43, 1.85)
Raltegravir + emtricitabine/ tenofovir DF	400 twice daily+200/300 once daily	400 once daily	100 once daily	30	sofosbuvir	1.09 (0.97, 1.23)	1.16 (1.07, 1.25)	NA
					GS-331007	0.95 (0.91, 0.98)	1.03 (1.00, 1.06)	1.08 (1.04, 1.13)
					velpatasvir	0.97 (0.87, 1.08)	0.98 (0.88, 1.10)	0.97 (0.87, 1.07)
Azole Anti-fungal								
Ketoconazole[f]	200 twice daily	ND	100 single dose	12	velpatasvir	1.29 (1.02, 1.64)	1.71 (1.35, 2.18)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	Velpatasvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007 and Velpatasvir PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
H2-Receptor Antagonists								
Famotidine	40 single dose simultaneously with EPCLUSA	400 single dose	100 single dose	60	sofosbuvir	0.92 (0.82, 1.05)	0.82 (0.74, 0.91)	NA
					GS-331007	0.84 (0.78, 0.89)	0.94 (0.91, 0.98)	NA
					velpatasvir	0.80 (0.70, 0.91)	0.81 (0.71, 0.91)	NA
	40 single dose 12 hours prior to EPCLUSA			60	sofosbuvir	0.77 (0.68, 0.87)	0.80 (0.73, 0.88)	NA
					GS-331007	1.20 (1.13, 1.28)	1.04 (1.01, 1.08)	NA
					velpatasvir	0.87 (0.76, 1.00)	0.85 (0.74, 0.97)	NA
Immunosuppressants								
Cyclosporine[f]	600 single dose	400 single dose	ND	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
		ND	100 single dose	12	velpatasvir	1.56 (1.22, 2.01)	2.03 (1.51, 2.71)	NA
Tacrolimus[f]	5 single dose	400 single dose	ND	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA
Opiate Agonist								
Methadone[f]	30 to 130 daily	400 once daily	ND	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	Velpatasvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007 and Velpatasvir PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Proton Pump Inhibitors								
Omeprazole	20 once daily simultaneously with EPCLUSA	400 single dose fasted	100 single dose fasted	60	sofosbuvir	0.66 (0.55, 0.78)	0.71 (0.60, 0.83)	NA
					GS-331007	1.18 (1.10, 1.26)	1.00 (0.95, 1.05)	NA
					velpatasvir	0.63 (0.50, 0.78)	0.64 (0.52, 0.79)	NA
	20 once daily 12 hours prior to EPCLUSA	400 single dose fasted	100 single dose fasted	60	sofosbuvir	0.55 (0.47, 0.64)	0.56 (0.49, 0.65)	NA
					GS-331007	1.26 (1.18, 1.34)	0.97 (0.94, 1.01)	NA
					velpatasvir	0.43 (0.35, 0.54)	0.45 (0.37, 0.55)	NA
	20 once daily 2 hours prior to EPCLUSA	400 single dose fed	100 single dose fed	40	sofosbuvir	0.84 (0.68, 1.03)	1.08 (0.94, 1.25)	NA
					GS-331007	0.94 (0.88, 1.02)	0.99 (0.96, 1.03)	NA
					velpatasvir	0.52 (0.43, 0.64)	0.62 (0.51, 0.75)	NA
	20 once daily 4 hours after EPCLUSA	400 single dose fed	100 single dose fed	38	sofosbuvir	0.79 (0.68, 0.92)	1.05 (0.94, 1.16)	NA
					GS-331007	0.91 (0.85, 0.98)	0.99 (0.95, 1.02)	NA
					velpatasvir	0.67 (0.58, 0.78)	0.74 (0.63, 0.86)	NA
	40 once daily 4 hours after EPCLUSA	400 single dose fed	100 single dose fed	40	sofosbuvir	0.70 (0.57, 0.87)	0.91 (0.76, 1.08)	NA
					GS-331007	1.01 (0.96, 1.07)	0.99 (0.94, 1.03)	NA
					velpatasvir	0.44 (0.34, 0.57)	0.47 (0.37, 0.60)	NA

NA = not available/not applicable, ND = not dosed.

a All interaction studies conducted in healthy volunteers.

b Administered as ATRIPLA® (efavirenz/emtricitabine/tenofovir DF fixed-dose combination).

c Administered as GENVOYA® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose single tablet regimen).

d Administered as STRIBILD® (elvitegravir/cobicistat/emtricitabine/tenofovir DF fixed-dose single tablet regimen).

e Administered as COMPLERA® (emtricitabine/rilpivirine/tenofovir DF fixed-dose combination).

f These studies have not been performed with EPCLUSA; they were conducted with either sofosbuvir or velpatasvir administered as single agents.

Table 9. Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Sofosbuvir, Velpatasvir, or EPCLUSA[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofos-buvir dose (mg)	Velpa-tasvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Sofosbuvir, Velpatasvir or EPCLUSA No Effect=1.00		
					C_{max}	AUC	C_{min}
Anti-HIV							
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF[b]	Atazanavir 300 once daily	400 once daily	100 once daily	24	1.09 (1.00, 1.19)	1.20 (1.10, 1.31)	1.39 (1.20, 1.61)
	Ritonavir 100 once daily				0.89 (0.82, 0.97)	0.97 (0.89, 1.05)	1.29 (1.15, 1.44)
	Emtricitabine 200 once daily				1.01 (0.96, 1.06)	1.02 (0.99, 1.04)	1.06 (1.02, 1.11)
	Tenofovir DF 300 once daily				1.55 (1.43, 1.68)	1.30 (1.24, 1.36)	1.39 (1.31, 1.48)
Darunavir/ ritonavir + emtricitabine/ tenofovir DF[c]	Darunavir 800 once daily	400 once daily	100 once daily	29	0.90 (0.86, 0.95)	0.92 (0.87, 0.98)	0.87 (0.79, 0.95)
	Ritonavir 100 once daily				1.07 (0.97, 1.17)	1.12 (1.05, 1.19)	1.09 (1.02, 1.15)
	Emtricitabine 200 once daily				1.05 (1.01, 1.08)	1.05 (1.02, 1.08)	1.04 (0.98, 1.09)
	Tenofovir DF 300 once daily				1.55 (1.45, 1.66)	1.39 (1.33, 1.44)	1.52 (1.45, 1.59)
Dolutegravir	50 once daily	400 once daily	100 once daily	24	1.06 (1.01, 1.11)	1.06 (1.01, 1.13)	1.04 (0.98, 1.10)
Efavirenz/ emtricitabine/ tenofovir DF[d]	Efavirenz 600 once daily	400 once daily	100 once daily	15	0.81 (0.74, 0.89)	0.85 (0.80, 0.91)	0.90 (0.85, 0.95)
	Emtricitabine 200 once daily				1.07 (0.98, 1.18)	1.07 (1.00, 1.14)	1.10 (0.97, 1.25)
	Tenofovir DF 300 once daily				1.77 (1.53, 2.04)	1.81 (1.68, 1.94)	2.21 (2.00, 2.43)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide[e]	Elvitegravir 150 once daily	400 once daily	100 once daily	24	0.87 (0.80, 0.94)	0.94 (0.88, 1.00)	1.08 (0.97, 1.20)
	Cobicistat 150 once daily				1.16 (1.09, 1.23)	1.30 (1.23, 1.38)	2.03 (1.67, 2.48)
	Emtricitabine 200 once daily				1.02 (0.97, 1.06)	1.01 (0.98, 1.04)	1.02 (0.97, 1.07)
	Tenofovir alafenamide 10 once daily				0.80 (0.68, 0.94)	0.87 (0.81, 0.94)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofos-buvir dose (mg)	Velpa-tasvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Sofosbuvir, Velpatasvir or EPCLUSA No Effect=1.00		
					C_{max}	AUC	C_{min}
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir DF[f]	Elvitegravir 150 once daily	400 once daily	100 once daily	24	0.93 (0.86, 1.00)	0.93 (0.87, 0.99)	0.97 (0.91, 1.04)
	Cobicistat 150 once daily				1.11 (1.06, 1.17)	1.23 (1.17, 1.29)	1.71 (1.54, 1.90)
	Emtricitabine 200 once daily				1.02 (0.97, 1.08)	1.01 (0.98, 1.04)	1.06 (1.01, 1.11)
	Tenofovir DF 300 once daily				1.36 (1.25, 1.47)	1.35 (1.29, 1.42)	1.45 (1.39, 1.51)
Emtricitabine/ rilpivirine/ tenofovir DF[g]	Emtricitabine 200 once daily	400 once daily	100 once daily	24	0.95 (0.90, 1.00)	0.99 (0.97, 1.02)	1.05 (0.99, 1.11)
	Rilpivirine 25 once daily				0.93 (0.88, 0.98)	0.95 (0.90, 1.00)	0.96 (0.90, 1.03)
	Tenofovir DF 300 once daily				1.44 (1.33, 1.55)	1.40 (1.34, 1.46)	1.84 (1.76, 1.92)
Lopinavir/ritonavir + emtricitabine/ tenofovir DF	Lopinavir 200 x 4 once daily	400 once daily	100 once daily	24	0.97 (0.92, 1.02)	1.00 (0.93, 1.06)	1.11 (0.96, 1.30)
	Ritonavir 50 x 4 once daily				0.94 (0.83, 1.07)	0.97 (0.89, 1.05)	1.07 (0.95, 1.20)
	Emtricitabine 200 once daily				1.02 (0.93, 1.12)	1.00 (0.94, 1.06)	0.97 (0.91, 1.04)
	Tenofovir DF 300 once daily				1.42 (1.27, 1.57)	1.22 (1.14, 1.31)	1.28 (1.20, 1.37)
Raltegravir + emtricitabine/ tenofovir DF	Emtricitabine 200 once daily	400 once daily	100 once daily	30	1.08 (1.04, 1.12)	1.05 (1.03, 1.07)	1.02 (0.97, 1.08)
	Tenofovir DF 300 once daily				1.46 (1.39, 1.54)	1.40 (1.34, 1.45)	1.70 (1.61, 1.79)
	Raltegravir 400 twice daily				1.03 (0.74, 1.43)	0.97 (0.73, 1.28)	0.79 (0.42, 1.48)
Cardiac Glycoside							
Digoxin	0.25 single dose	ND	100 once daily	21	1.88 (1.71, 2.08)	1.34 (1.13, 1.60)	NA
Estrogen-based Contraceptives							
Norelgestromin[h]	Norgestimate 0.180/0.215/ 0.250/ethinyl estradiol 0.025 once daily	ND	100 once daily	13	0.97 (0.88, 1.07)	0.90 (0.82, 0.98)	0.92 (0.83, 1.03)
		400 once daily	ND	15	1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofos-buvir dose (mg)	Velpa-tasvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Sofosbuvir, Velpatasvir or EPCLUSA No Effect=1.00		
					C_{max}	AUC	C_{min}
Norgestrel[h]		ND	100 once daily	13	0.96 (0.78, 1.19)	0.91 (0.73, 1.15)	0.92 (0.73, 1.18)
		400 once daily	ND	15	1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol[h]		ND	100 once daily	12	1.39 (1.17, 1.66)	1.04 (0.87, 1.24)	0.83 (0.65, 1.06)
		400 once daily	ND	15	1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Immunosuppressants							
Cyclosporine[h]	600 single dose	400 single dose	ND	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
		ND	100 single dose	12	0.92 (0.82, 1.02)	0.88 (0.78, 1.00)	NA
Tacrolimus[h]	5 single dose	400 single dose	ND	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Opiate Agonists							
R-Methadone[h]	30 to 130 daily	400 once daily	ND	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone[h]					0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)
Statins							
Pravastatin[h]	40 single dose	ND	100 once daily	18	1.28 (1.08, 1.52)	1.35 (1.18, 1.54)	NA
Rosuvastatin[h]	10 single dose	ND	100 once daily	18	2.61 (2.32, 2.92)	2.69 (2.46, 2.94)	NA

NA = not available/not applicable, ND = not dosed.

a All interaction studies conducted in healthy volunteers.

b Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.

c Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.

d Administered as ATRIPLA (efavirenz, emtricitabine and tenofovir DF fixed-dose combination).

e Administered as GENVOYA (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide fixed-dose single tablet regimen).

f Administered as STRIBILD (elvitegravir, cobicistat, emtricitabine and tenofovir DF fixed-dose single tablet regimen).

g Administered as COMPLERA (emtricitabine, rilpivirine and tenofovir DF fixed-dose combination).

h These studies have not been performed with EPCLUSA; they were conducted with either sofosbuvir or velpatasvir administered as single agents.

Drug-Food Interactions

No interactions between EPCLUSA and food have been identified.

Drug-Herb Interactions

St. John's wort should not be used with EPCLUSA.

Coadministration of St. John's wort, a potent P-gp and CYP inducer, may decrease sofosbuvir and velpatasvir plasma concentrations, which may result in loss of therapeutic effect. See **WARNINGS AND PRECAUTIONS**, **General, Use with Potent P-gp Inducers and/or Potent or Moderate CYP Inducers**.

Drug-Laboratory Interactions

Interactions of EPCLUSA with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

EPCLUSA is a single tablet regimen. No dosage adjustments are possible for EPCLUSA.

The recommended dose of EPCLUSA is one tablet of 400 mg/100 mg sofosbuvir/velpatasvir, taken orally, once daily with or without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, *Effects of Food***).

The recommended dose and treatment duration for EPCLUSA is provided in Table 10.

Table 10. Recommended Treatment Regimen (All HCV Genotypes)

Patient Population	Recommended Dose and Duration of Treatment
Patients without cirrhosis and patients with compensated cirrhosis	EPCLUSA one tablet daily for 12 weeks
Patients with decompensated cirrhosis[a]	EPCLUSA one tablet daily + ribavirin[b] for 12 weeks

a Limited data for genotypes 2, 4, 5 and 6 (see **WARNINGS AND PRECAUTIONS**, and **CLINICAL TRIALS**)

b When administered with EPCLUSA, the recommended dose of ribavirin is based on weight: 1000 mg per day for patients less than 75 kg and 1200 mg for those weighing at least 75 kg, divided and administered twice daily with food. For ribavirin dose modifications, refer to the Product Monograph containing ribavirin information.

Special Populations

Pediatrics (< 18 Years of age)

EPCLUSA is not indicated for use in pediatric patients < 18 years of age.

Geriatrics (≥ 65 years of age)

No dose adjustment is warranted for elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatic Impairment

No dose adjustment of EPCLUSA is required for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). Based on pharmacokinetic data, no dose adjustment of EPCLUSA is required for patients with Child-Pugh Class C hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**). However, safety and efficacy of EPCLUSA have not been established in patients with Child-Pugh Class C decompensated cirrhosis.

Renal Impairment

No dose adjustment of EPCLUSA is required for patients with mild or moderate renal impairment. The safety and efficacy of EPCLUSA has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or ESRD requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY**).

Missed Dose

If a patient misses a dose of EPCLUSA within 18 hours of the time it is usually taken, the patient should take EPCLUSA as soon as possible, and then take the next dose of EPCLUSA at the regularly scheduled time.

If a patient misses a dose of EPCLUSA and it is after 18 hours of the time it is usually taken, the patient should not take the missed dose, but resume the usual dosing schedule. A double dose of EPCLUSA must not be taken.

If a patient vomits less than 3 hours after taking a dose of EPCLUSA, the patient should take another dose of EPCLUSA. If a patient vomits more than 3 hours after taking a dose of EPCLUSA, the patient should take the next dose at the regularly scheduled time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Administration of activated charcoal may be used to aid in the removal of unabsorbed active substance. General supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient are recommended.

No specific antidote is available for overdose with EPCLUSA. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with EPCLUSA consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Hemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Hemodialysis is unlikely to result in significant removal of velpatasvir since velpatasvir is highly bound to plasma protein.

The highest documented doses of sofosbuvir and velpatasvir were a single dose of 1200 mg and a single dose of 500 mg, respectively. In these healthy volunteer studies, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

ACTION AND CLINICAL PHARMACOLOGY

Description

EPCLUSA is a fixed-dose single tablet regimen of sofosbuvir and velpatasvir.

Sofosbuvir is a nucleotide analog pan-genotypic NS5B polymerase inhibitor. Velpatasvir is a pan-genotypic HCV NS5A inhibitor.

Mechanism of Action

EPCLUSA

Both sofosbuvir and velpatasvir exhibit high potency and specificity as individual agents against HCV as compounds that target the HCV NS5B and NS5A proteins respectively. Both compounds display low cytotoxicity in a number of distinct cell lines and display no significant antiviral activity against other viruses tested. *In vitro* combination studies using both sofosbuvir and velpatasvir showed an additive effect as measured by *in vitro* cell based HCV replicon assays, with no antagonism detected. As individual components, both sofosbuvir and velpatasvir showed additive to synergistic activity with all other anti-HCV agents.

Sofosbuvir

Sofosbuvir is a pan-genotypic polymerase inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Sofosbuvir is a monophosphorylated pyrimidine nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203).

Velpatasvir

Velpatasvir is a pan-genotypic HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. *In vitro* resistance selection and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

Pharmacodynamics

Effect on Electrocardiogram

The effects of administration of supratherapeutic doses of sofosbuvir (1200 mg) and velpatasvir (500 mg) (as individual drugs) demonstrated a lack of effect of sofosbuvir or velpatasvir on QTc interval.

Pharmacokinetics

Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg. Velpatasvir AUC increases in a greater than proportional manner from 5 to 50 mg and in a less than proportional manner from 50 to 450 mg, indicating velpatasvir absorption is solubility limited.

The pharmacokinetics of EPCLUSA are shown in Table 11.

Table 11. Summary of Pharmacokinetics for Once-Daily Administration of EPCLUSA in Healthy Adult Subjects and HCV-Infected Patients

PK Parameters	Healthy Subjects[a] EPCLUSA N = 331 Geometric Mean (Range)			HCV-Infected Patients[b] EPCLUSA N = 1428 Geometric Mean (Range)		
	SOF	GS-331007	VEL	SOF[c]	GS-331007	VEL[d]
AUC_{0-24} (ng·h/mL)	1272 (543, 2348)	12040 (6983, 20488)	4556 (612, 12185)	1262 (337, 5333)	13967 (5217, 44182)	2967 (603, 11503)
C_{max} (ng/mL)	550 (187, 1171)	817 (453, 1448)	421 (47, 1066)	566 (143, 1582)	868 (284, 2113)	259 (39, 977)
C_{min} (ng/mL)	ND	ND	65 (9, 243)	ND	ND	41 (5, 236)

ND = not determined; SOF = sofosbuvir; VEL = velpatasvir
a. Population PK analysis from Phase 1 studies.
b. Population PK analysis from Phase 2 and 3 studies.
c. N=982; 446 patients did not have estimable PK parameters for SOF
d. N=1425; 3 patients did not have estimable PK parameters for VEL

Based on population PK analyses, sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and patients with HCV infection. Relative to healthy subjects (N=331), velpatasvir AUC_{0-24} and C_{max} were 37% lower and 41% lower, respectively, in HCV-infected patients. Age, race, BMI, HCV genotype or the presence or absence of cirrhosis had no clinically relevant effects on the exposure of sofosbuvir, GS-331007, or velpatasvir.

Absorption

Following oral administration of EPCLUSA, sofosbuvir median peak plasma concentration was observed 0.5-1.0 hour post-dose. Median peak plasma concentration of GS-331007 was observed between 3.0 hours post-dose. Velpatasvir median peak concentrations were observed 3.0 hours post-dose.

Effects of Food

Relative to fasting conditions, the administration (to healthy subjects) of a single dose of EPCLUSA with a moderate fat (~600 kcal, 30% fat) or high fat (~800 kcal, 50% fat) meal delayed the absorption of both sofosbuvir (median t_{max} delayed from 0.5 hours to 2.0 hours) and velpatasvir (median t_{max} delayed from 3.0 hours to 4.0 hours).

The extent of sofosbuvir absorption was significantly higher when administered with food (AUC increased 60% and 78% with a moderate fat or a high fat meal, respectively) and the C_{max} was unchanged. Food did not alter GS-331007 AUC but resulted in a 25% and 37% decrease in C_{max}, when EPCLUSA was administered with a moderate fat or a high fat meal, respectively.

The extent of velpatasvir absorption was increased more with a moderate fat meal (AUC increased 35% and C_{max} increased 31%) than with a high fat meal (AUC increased by 22% and no significant change in C_{max}).

The response rates in Phase 3 trials were similar in HCV-infected patients who received EPCLUSA with food or without food. EPCLUSA can be administered without regard to food.

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Velpatasvir is > 99.5% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09 μg/mL to 1.8 μg/mL. After a single 100 mg dose of [^{14}C]-velpatasvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity ranged between 0.52 and 0.67.

Metabolism

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate, GS-461203. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for greater than 90% of total systemic exposure.

In vitro, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed. Following a single dose of 100 mg [^{14}C]-velpatasvir to healthy human male subjects, the majority (> 98%) of radioactivity in plasma was the parent drug. Unchanged velpatasvir is the major species present in feces.

Excretion

Sofosbuvir is primarily eliminated in the urine as GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of EPCLUSA were 0.5 and 25 hours, respectively.

Biliary excretion of parent drug was the major route of elimination for velpatasvir. The median terminal half-life of velpatasvir following administration of EPCLUSA was approximately 15 hours.

Special Populations and Conditions

Pediatrics (< 18 years of age)

The pharmacokinetics of sofosbuvir, GS-331007 and velpatasvir in pediatric patients have not been established.

Geriatrics (≥ 65 years of age)

Based on population pharmacokinetic analyses, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007 or velpatasvir. Clinical studies of EPCLUSA included 156 patients aged 65 and over. The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

Gender

No clinically relevant pharmacokinetic differences due to gender have been identified for sofosbuvir, GS-331007, or velpatasvir.

Race

No clinically relevant pharmacokinetic differences due to race have been identified for sofosbuvir, GS-331007, or velpatasvir.

Hepatic Insufficiency

Hepatic impairment studies were conducted with the individual drugs, sofosbuvir and velpatasvir.

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Mild hepatic impairment is not expected to meaningfully alter the pharmacokinetics of sofosbuvir and GS-331007. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with moderate and severe hepatic impairment (Child Pugh Class B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in subjects with moderate hepatic impairment, severe hepatic impairment, and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of velpatasvir.

Renal Insufficiency

Renal impairment studies have been conducted with the individual drugs, sofosbuvir and velpatasvir.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR $\geq$ 50 and < 80 mL/min/1.73m^2), moderate (eGFR $\geq$ 30 and < 50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir (N=6/group). Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir AUC_{inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{inf} was 55%, 88% and 451% higher, respectively. In subjects with ESRD, sofosbuvir AUC_{inf} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis. The AUC_{inf} of GS-331007 in subjects with ESRD administered sofosbuvir 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively, compared to normal subjects.

Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. Following a single 400 mg dose of sofosbuvir, a 4 hour hemodialysis session removed approximately 18% of administered dose.

Velpatasvir is primarily excreted in feces. Exposure of velpatasvir is not significantly impacted in the setting of severe renal impairment. The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Velpatasvir AUC and C_{max} were approximately 50%

and 11% higher, respectively, in subjects with severe renal impairment compared to control subjects with normal renal function; these differences are not considered clinically relevant.

STORAGE AND STABILITY

Store below 30 °C (86 °F).

- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

EPCLUSA is a single tablet regimen containing sofosbuvir and velpatasvir for oral administration.

Each tablet contains 400 mg of sofosbuvir and 100 mg of velpatasvir. The tablets include the following inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: iron oxide red, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

EPCLUSA is available as a pink colored, diamond shaped, film-coated tablet debossed with “GSI” on one side and “7916” on the other side of the tablet. Each bottle contains 28 tablets, a polyester coil and closed with a child resistant closure.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

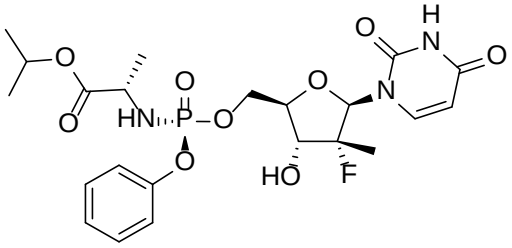
Proper name: **sofosbuvir**

Chemical name: (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate

Molecular formula: $C_{22}H_{29}FN_3O_9P$

Molecular mass: 529.45

Structural formula:



Physicochemical properties:

Appearance: Sofosbuvir is a white to off-white crystalline solid.

Solubility: Sofosbuvir is slightly soluble in water.

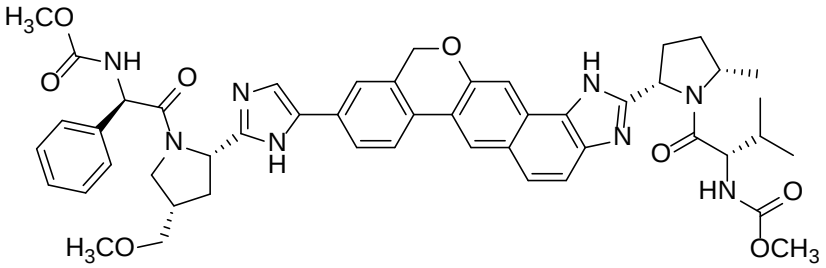
Proper name: **velpatasvir**

Chemical name: Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Molecular formula: $C_{49}H_{54}N_8O_8$

Molecular mass: 883.00

Structural formula:



Physicochemical properties:

Appearance	Velpatasvir is a white to tan or yellow solid.
Solubility	Velpatasvir is practically insoluble (< 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2.0, and soluble (> 36 mg/mL) at pH 1.2.

CLINICAL TRIALS

The efficacy of EPCLUSA was evaluated in three Phase 3 trials with data available for a total of 1035 patients with genotype 1 to 6 chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis. The efficacy of EPCLUSA was also evaluated in one Phase 3 trial in 267 patients with HCV infection with decompensated cirrhosis (ASTRAL-4).

Sustained virologic response (SVR), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint to determine the HCV cure rate.

The demographics and baseline characteristics for the patients in studies ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4 were balanced across the treatment groups for each study and are summarized in Table 13, Table 17, Table 21, and Table 25, respectively.

The ribavirin (RBV) dose was weight-based (1,000 mg daily administered in two divided doses for patients < 75 kg and 1,200 mg for those ≥ 75 kg) and administered in two divided doses when used in combination with sofosbuvir in the ASTRAL-2 and ASTRAL-3 trials or in combination with EPCLUSA in the ASTRAL-4 trial. RBV dose adjustments were performed according to the Product Monograph for RBV. Serum HCV RNA values were measured during the clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU per mL.

Clinical Trials in Patients with Compensated Liver Disease

Genotypes 1, 2, 4, 5, 6 HCV Infected Adults (ASTRAL-1)

Trial Design

Table 12. Summary of Trial Design in Genotypes 1, 2, 4, 5, 6 HCV Patients with or without Cirrhosis (ASTRAL-1)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, double-blind, placebo-controlled, multicentre	EPCLUSA (400 mg/100 mg), QD, PO or Placebo, QD, PO	EPCLUSA	12 weeks
		Placebo	12 weeks

PO = orally; QD = once a day

Patients with genotype 1, 2, 4, or 6 HCV were randomized in a 5:1 ratio to treatment with EPCLUSA for 12 weeks or placebo for 12 weeks. Patients with genotype 5 HCV were enrolled to the EPCLUSA group. Randomization was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) and the presence or absence of cirrhosis.

Demographics and Other Baseline Characteristics

Table 13. Demographic and Other Baseline Characteristics of Genotypes 1, 2, 4, 5, 6 HCV Patients with or without Cirrhosis (ASTRAL-1)

Characteristics	EPCLUSA 12 Weeks N = 624	Placebo 12 Weeks N = 116
Age (years)		
Mean (range)	54 (18-82)	53 (25-74)
Gender, n (%)		
Male	374 (60)	68 (59)
Female	250 (40)	48 (41)
Race, n (%*)		
White	493 (79)	90 (78)
Black	52 (8)	11 (9)
Asian	62 (10)	11 (9)
Other	14 (2)	4 (3)
Not disclosed	3 (< 1)	0
BMI, n (%)		
< 30 kg/m^2	489 (78)	93 (80)
≥ 30 kg/m^2	135 (22)	23 (20)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.3 ± 0.7	6.3 ± 0.6
< 800,000 copies/mL, n (%)	163 (26)	29 (25)
≥ 800,000 copies/mL, n (%)	461 (74)	87 (75)

Characteristics	EPCLUSA 12 Weeks N = 624	Placebo 12 Weeks N = 116
HCV genotype, n (%*)		
1	328 (53)	65 (56)
1a	210 (34)	46 (40)
1b	118 (19)	19 (16)
2	104 (17)	21 (18)
4	116 (19)	22 (19)
5	35 (6)	0
6	41 (7)	8 (7)
IL28B, n (%*)		
CC	186 (30)	36 (31)
Non-CC	433 (69)	79 (68)
Missing	5 (< 1)	1 (< 1)
Cirrhosis, n (%*)		
Yes (compensated)	121 (19)	21 (18)
No	501 (80)	95 (82)
Missing	2 (< 1)	0
Treatment Status, n (%)		
Treatment-naïve	423 (68)	83 (72)
Treatment experienced	201 (32)	33 (28)
Prior HCV Treatment, n (%)		
DAA+Peg-IFN+RBV	56/201 (28)	6/33 (18)
Peg-IFN+RBV	122/201 (61)	24/33 (73)
Other	23/201 (11)	3/33 (9)
Prior HCV Response, n (%*)		
Nonresponder	96/201 (48)	14/33 (42)
Relapse/Breakthrough	103/201 (51)	19/33 (58)
Not applicable	2/201 (< 1)	0/33

DAA = direct acting antiviral; Peg-IFN = pegylated interferon; RBV= ribavirin; SD = standard deviation
*Total percentage may not add to 100% due to rounding.

Study Results

The response rates for the EPCLUSA treatment group by HCV genotypes in the ASTRAL-1 trial are presented in Table 14. The EPCLUSA 12 Week group met the primary endpoint of an SVR12 rate that was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$). No patient in the EPCLUSA 12 Week group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse). No patient in the placebo group achieved SVR12.

Table 14. SVR12 and Virologic Failure in Genotypes 1, 2, 4, 5, 6 HCV Infected Patients with or without Cirrhosis (ASTRAL-1)

	EPCLUSA 12 weeks (N = 624)							
	Total (all GTs) (N=624) % (n/N)	**GT-1**			**GT-2 (N=104) % (n/N)**	**GT-4 (N=116) % (n/N)**	**GT-5 (N=35) % (n/N)**	**GT-6 (N=41) % (n/N)**
		GT-1a (N=210) % (n/N)	**GT-1b (N=118) % (n/N)**	**Total (N=328) % (n/N)**				
SVR12[a]	99 (618/624)	98 (206/210)	99 (117/118)	98 (323/328)	100 (104/104)	100 (116/116)	97 (34/35)	100 (41/41)
Outcome for Patients without SVR								
Overall Virologic Failure	< 1 (2/624)	< 1 (1/210)	< 1 (1/118)	< 1 (2/328)	0/104	0/116	0/35	0/41
On-Treatment Virologic Failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapse[b]	< 1 (2/623)	< 1 (1/209)	< 1 (1/118)	< 1 (2/327)	0/104	0/116	0/35	0/41
Other[c]	< 1 (4/624)	< 1 (3/210)	0/118	< 1 (3/328)	0/104	0/116	3 (1/35)	0/41

GT = genotype

a SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 15 IU/mL) at 12 weeks after the cessation of treatment.

b The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.

c Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 15.

Table 15. Sustained Virologic Response (SVR) for Select Subgroups of Genotypes 1, 2, 4, 5, 6 HCV Patients with or without Cirrhosis (ASTRAL-1)

	EPCLUSA 12 weeks (N = 624)							
	Total (all GTs) (N=624)	GT-1			GT-2 (N=104)	GT-4 (N=116)	GT-5 (N=35)	GT-6 (N=41)
		GT-1a (N=210)	GT-1b (N=118)	Total (N=328)				
	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)
Cirrhosis								
Yes (compensated)	99 (120/121)	100 (49/49)	96 (23/24)	99 (72/73)	100 (10/10)	100 (27/27)	100 (5/5)	100 (6/6)
No	99 (496/501)	98 (157/161)	100 (94/94)	98 (251/255)	100 (93/93)	100 (89/89)	97 (28/29)	100 (35/35)
Missing	100 (2/2)	0/0	0/0	0/0	100 (1/1)	0/0	100 (1/1)	0/0
Prior HCV Treatment Experience								
Treatment-naïve	99 (418/423)	97 (128/132)	100 (86/86)	98 (214/218)	100 (79/79)	100 (64/64)	96 (23/24)	100 (38/38)
Treatment experienced	> 99 (200/201)	100 (78/78)	97 (31/32)	99 (109/110)	100 (25/25)	100 (52/52)	100 (11/11)	100 (3/3)

GT = genotype

High SVR12 rates were achieved in all subgroups across all HCV genotypes. All patients previously treated with a direct acting antiviral (DAA) + Peg-IFN+RBV achieved SVR12 (56 of 56, 100%), which included 48, 6, and 2 patients with genotype 1, 4, and 5 HCV infection, respectively.

Genotype 2 HCV Infected Adults (ASTRAL-2)

Trial Design

Table 16. Summary of Trial Design in Genotype 2 HCV Patients with or without Cirrhosis (ASTRAL-2)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	EPCLUSA (400 mg/100 mg), QD, PO or SOF 400 mg QD + RBV 1000 or 1200 mg/day, BID, PO	EPCLUSA	12 weeks
		SOF+RBV	12 weeks

BID = twice a day; PO = orally; QD = once a day; RBV = ribavirin; SOF = sofosbuvir

Patients were randomized in a 1:1 ratio to treatment with EPCLUSA for 12 weeks or SOF+RBV for 12 weeks. Randomization was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve vs treatment experienced).

Demographic and Baseline Characteristics

Table 17. Demographic and Other Baseline Characteristics of Genotype 2 HCV Patients with or without Cirrhosis (ASTRAL-2)

Characteristics	EPCLUSA 12 Weeks N = 134	SOF+RBV 12 Weeks N = 132
Age (years)		
Mean (range)	57 (26–81)	57 (23-76)
Gender, n (%)		
Male	86 (64)	72 (55)
Female	48 (36)	60 (45)
Race, n (%*)		
White	124 (93)	111 (84)
Black	6 (4)	12 (9)
Asian	1 (< 1)	5 (4)
Other	1 (< 1)	3 (2)
Not disclosed	2 (1)	1 (< 1)
BMI, n (%)		
< 30 kg/m^2	95 (71)	84 (64)
≥ 30 kg/m^2	39 (29)	48 (36)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.5 ± 0.8	6.4 ± 0.7
< 800,000 copies/mL, n (%)	23 (17)	31 (23)
≥ 800,000 copies/mL, n (%)	111 (83)	101 (77)
HCV genotype, n (%)		
2	134 (100)	132 (100)
2 (no confirmed subtype)	13 (10)	12 (9)
2a	2 (1)	4 (3)
2a/2c	16 (12)	12 (9)
2b	103 (77)	104 (79)
IL28B, n (%)		
CC	55 (41)	46 (35)
Non-CC	79 (59)	86 (65)
Cirrhosis, n (%*)		
Yes (compensated)	19 (14)	19 (14)
No	115 (86)	112 (85)
Missing	0	1 (< 1)
Prior HCV Treatment Experience, n (%)		
Treatment-naïve	115 (86)	112 (85)
Treatment experienced	19 (14)	20 (15)
Prior HCV Treatment, n (%)		
Peg-IFN+RBV	16/19 (84)	15/20 (75)
Other	3/19 (16)	5/20 (25)

Characteristics	EPCLUSA 12 Weeks N = 134	SOF+RBV 12 Weeks N = 132
Prior HCV Response, n (%)		
Nonresponder	3/19 (16)	3/20 (15)
Relapse/Breakthrough	16/19 (84)	17/20 (85)

Peg-IFN = pegylated interferon; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir
*Total percentage may not add to 100% due to rounding.

Study Results

The response rates for the treatment groups in the ASTRAL-2 trial are presented in Table 18. Treatment with EPCLUSA for 12 weeks demonstrated statistical superiority (p = 0.018) compared to treatment with SOF+RBV for 12 weeks (treatment difference +5.2%; 95% confidence interval: +0.2% to +10.3%).

Table 18. SVR12 and Virologic Failure in Genotype 2 HCV Infected Patients with or without Cirrhosis (ASTRAL-2)

	EPCLUSA 12 Weeks N = 134 % (n/N)	SOF+RBV 12 Weeks N = 132 % (n/N)
SVR12[a]	99 (133/134)	94 (124/132)
Outcome for patients without SVR		
Overall Virologic Failure	0/134	5 (6/132)
On-Treatment Virologic Failure	0/134	0/132
Relapse[b]	0/133	5 (6/132)
Other[c]	< 1 (1/134)	2 (2/132)

RBV = ribavirin; SOF = sofosbuvir
a. SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ at 12 weeks (Lower Limit of Quantitation, 15 IU/mL) after the cessation of treatment.
b. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 19.

Table 19. Sustained Virologic Response (SVR) for Select Subgroups of Genotype 2 HCV Patients with or without Cirrhosis (ASTRAL-2)

Study Outcomes	EPCLUSA 12 Weeks N = 134 % (n/N)	SOF+RBV 12 Weeks N = 132 % (n/N)
Genotype[a]		
2 (no confirmed subtype)	100 (13/13)	92 (11/12)
2a	100 (2/2)	100 (4/4)
2a/2c	100 (16/16)	92 (11/12)
2b	99 (102/103)	94 (98/104)
Cirrhosis		
Yes (compensated)	100 (19/19)	95 (18/19)
No	99 (114/115)	94 (105/112)
Missing	0/0	100 (1/1)
Prior HCV Treatment Experience		
Treatment-naïve	99 (114/115)	96 (107/112)
Treatment experienced	100 (19/19)	85 (17/20)
Nonresponder	100 (3/3)	67 (2/3)
Relapse/Breakthrough	100 (16/16)	88 (15/17)

RBV = ribavirin; SOF = sofosbuvir

Genotype 3 HCV Infected Adults (ASTRAL-3)

Trial Design

Table 20. Summary of Trial Design in Genotype 3 HCV Patients with or without Cirrhosis (ASTRAL-3)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	EPCLUSA (400 mg/100 mg), QD, PO	EPCLUSA	12 weeks
	SOF 400 mg QD, PO + RBV 1000 or 1200 mg/day, BID, PO	SOF+RBV	24 weeks

BID = twice a day; PO = orally; QD = once a day; RBV = ribavirin; SOF = sofosbuvir

Patients were randomized in a 1:1 ratio to treatment with EPCLUSA for 12 weeks or SOF+RBV for 24 weeks. Randomization was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve vs treatment experienced).

Demographics and Other Baseline Characteristics

Table 21. Demographic and Other Baseline Characteristics of Genotype 3 HCV Patients with or without Cirrhosis (ASTRAL-3)

Characteristics	EPCLUSA 12 Weeks N = 277	SOF+RBV 24 Weeks N = 275
Age (years)		
Mean (range)	49 (21–76)	50 (19–74)
Gender, n (%)		
Male	170 (61)	174 (63)
Female	107 (39)	101 (37)
Race, n (%*)		
White	250 (90)	239 (87)
Black	3 (1)	1 (< 1)
Asian	23 (8)	29 (11)
Other	1 (< 1)	5 (2)
Not disclosed	0	1 (< 1)
BMI, n (%)		
< 30 kg/m^2	226 (82)	214 (78)
≥ 30 kg/m^2	51 (18)	61 (22)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.2 ± 0.7	6.3 ± 0.7
< 800,000 copies/mL, n (%)	86 (31)	81 (29)
≥ 800,000 copies/mL, n (%)	191 (69)	194 (71)
HCV genotype, n (%*)		
3	277 (100)	275 (100)
3a	265 (96)	250 (91)
3b	2 (< 1)	5 (2)
3h	0	2 (< 1)
3k	1 (< 1)	0
3 (no confirmed subtype)	9 (3)	18 (7)
IL28B, n (%)		
CC	105 (38)	111 (40)
Non-CC	172 (62)	164 (60)
Cirrhosis, n (%)		
Yes (compensated)	80 (29)	83 (30)
No	197 (71)	187 (68)
Missing	0	5 (2)
Prior HCV Treatment Experience, n (%)		
Treatment-naïve	206/277 (74)	204/275 (74)
Treatment experienced	71/277 (26)	71/275 (26)
Prior HCV Treatment, n (%*)		
DAA+Peg-IFN+RBV	1/71 (1)	0/71
Peg-IFN+RBV	64/71 (90)	65/71 (92)
Other	6/71 (8)	6/71 (8)
Prior HCV Response, n (%)		
Nonresponder	20/71 (28)	24/71 (34)
Relapse/Breakthrough	51/71 (72)	47/71 (66)

DAA = direct acting antiviral; Peg-IFN = pegylated interferon; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir
*Total percentage may not add to 100% due to rounding.

Study Results

The response rates for the treatment groups in study ASTRAL-3 are presented in Table 22. Treatment with EPCLUSA for 12 weeks demonstrated statistical superiority ($p < 0.001$) compared to treatment with SOF+RBV for 24 weeks (treatment difference +14.8%; 95% confidence interval: +9.6% to +20.0%).

Table 22. SVR12 and Virologic Failure in Genotype 3 HCV Infected Patients with or with Cirrhosis (ASTRAL-3)

	EPCLUSA 12 Weeks N = 277 % (n/N)	**SOF+RBV 24 Weeks N = 275 % (n/N)**
SVR12[a]	95 (264/277)	80 (221/275)
Overall Virologic Failure	4 (11/277)	14 (39/275)
On-Treatment Virologic Failure	0/277	< 1 (1/275)
Relapse[b]	4 (11/276)	14 (38/272)
Other[c]	< 1 (2/277)	5 (15/275)

RBV = ribavirin; SOF = sofosbuvir

a. SVR12, Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 15 IU/mL) at 12 weeks after the cessation of treatment.
b. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

Response rates for selected subgroups are presented in Table 23.

Table 23. Sustained Virologic Response (SVR) for Select Subgroups of Genotype 3 HCV Patients with or without Cirrhosis (ASTRAL-3)

Study Outcomes	**EPCLUSA 12 Weeks N = 277 % (n/N)**	**SOF +RBV 24 Weeks N = 275[a] % (n/N)**
Genotype		
3a	95 (253/265)	80 (199/250)
3b	100 (2/2)	100 (5/5)
3h	0	100 (2/2)
3k	100 (1/1)	0
3 (no confirmed subtype)	89 (8/9)	83 (15/18)
Cirrhosis by Prior HCV Treatment Experience		
Treatment-Naïve		
With Cirrhosis (compensated)	93 (40/43)	73 (33/45)
Without Cirrhosis	98 (160/163)	90 (141/156)
Missing	0/0	67 (2/3)
Treatment Experienced		
With Cirrhosis (compensated)	89 (33/37)	58 (22/38)
Without Cirrhosis	91 (31/34)	71 (22/31)

Study Outcomes	EPCLUSA 12 Weeks N = 277 % (n/N)	SOF +RBV 24 Weeks N = 275[a] % (n/N)
Missing	0/0	50 (1/2)
Response to Prior HCV Therapy		
Non-Responder	85 (17/20)	58 (14/24)
Relapse/Breakthrough	92 (47/51)	66 (31/47)
Prior HCV Therapy		
DAA+PEG-IFN+RBV	100 (1/1)	0
PEG-IFN+RBV	89 (57/64)	63 (41/65)
Other	100 (6/6)	67 (4/6)

DAA = direct acting antiviral; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

a. Five patients with missing cirrhosis status in the SOF+RBV 24 Week group were excluded from this subgroup analysis.

The overall SVR12 (virologic cure) across the three trials (ASTRAL-1, ASTRAL-2, ASTRAL-3) was 98% (1015/1035).

Clinical Trial in Patients with Decompensated Cirrhosis (ASTRAL-4)

Trial Design

Table 24. Summary of Trial Design in HCV Patients with Decompensated Cirrhosis (ASTRAL-4)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	EPCLUSA (400 mg/100 mg), QD, PO	EPCLUSA	12 weeks
	EPCLUSA (400 mg/100 mg), QD, PO + RBV 1000 or 1200 mg/day, BID, PO	EPCLUSA + RBV	12 weeks
	EPCLUSA (400 mg/100 mg), QD, PO	EPCLUSA	24 weeks

BID = twice a day; PO = orally; QD = once a day; RBV = ribavirin; SOF = sofosbuvir

Patients were randomized in a 1:1:1 ratio to treatment with EPCLUSA for 12 weeks, EPCLUSA + RBV for 12 weeks or EPCLUSA for 24 weeks. Randomization was stratified by HCV genotype (1, 2, 3, 4, 5, 6, and indeterminate). No patients with genotype 5 HCV infection were enrolled.

Demographics and Other Baseline Characteristics

Table 25. Demographic and Other Baseline Characteristics of HCV Patients with Decompensated Cirrhosis (ASTRAL-4)

Characteristics	EPCLUSA 12 Weeks N = 90	EPCLUSA + RBV 12 Weeks N = 87	EPCLUSA 24 Weeks N = 90
Age (years)			
Mean (range)	58 (42–73)	58 (40-71)	58 (46-72)
Gender, n (%)			
Male	57 (63)	66 (76)	63 (70)
Female	33 (37)	21 (24)	27 (30)
Race, n (%)			
White	79 (88)	79 (91)	81 (90)
Black	6 (7)	5 (6)	6 (7)
Asian	3 (3)	0	2 (2)
Other	2 (2)	3 (3)	0
Not disclosed	0	0	1 (1)
BMI, n (%)			
< 30 kg/m^2	48 (53)	54 (62)	52 (58)
≥ 30 kg/m^2	42 (47)	33 (38)	38 (42)
Viral Load			
HCV RNA Log10 IU/mL, mean ± SD	6.0 ± 0.5	5.8 ± 0.6	5.9 ± 0.6
< 800,000 copies/mL, n (%)	31 (34)	42 (48)	45 (50)
≥ 800,000 copies/mL, n (%)	59 (66)	45 (52)	45 (50)
HCV genotype, n (%*)			
1	68 (76)	68 (78)	71 (79)
1a	50 (56)	54 (62)	55 (61)
1b	18 (20)	14 (16)	16 (18)
2	4 (4)	4 (5)	4 (4)
3	14 (16)	13 (15)	12 (13)
4	4 (4)	2 (2)	2 (2)
6	0	0	1 (1)
IL28B, n (%)			
CC	20 (22)	22 (25)	20 (22)
Non-CC	70 (78)	65 (75)	68 (76)
Missing	0	0	2 (2)
Baseline CPT Score Category, n (%*)			
CPT A [5-6]	3 (3)	6 (7)	7 (8)
CPT B [7-9]	86 (96)	77 (89)	77 (86)
CPT C [10-12]	1 (1)	4 (5)	6 (7)
Baseline MELD Score Category, n (%*)			
< 10	36 (40)	29 (33)	26 (29)
10-15	50 (56)	54 (62)	59 (66)
16-20	3 (3)	4 (5)	5 (6)
21-25	1 (1)	0	0
Prior HCV Treatment Experience, n (%*)			
Treatment-naïve	32 (36)	40 (46)	48 (53)
Treatment experienced	58 (64)	47 (54)	42 (47)
DAA+Peg-IFN+RBV	9/58 (16)	12/47 (26)	7/42 (17)
Peg-IFN+RBV	30/58 (52)	27/47 (57)	28/42 (67)
Other	18/58 (31)	8/47 (17)	7/42 (17)
Missing	1/58 (2)	0	0

Characteristics	EPCLUSA 12 Weeks N = 90	EPCLUSA + RBV 12 Weeks N = 87	EPCLUSA 24 Weeks N = 90
Prior HCV Response, n (%*)			
Nonresponder	38/58 (66)	33/47 (70)	27/42 (64)
Relapse/Breakthrough	15/58 (26)	10/47 (21)	12/42 (29)
Not Applicable	4/58 (7)	4/47 (9)	3/42 (7)
Missing	1/58 (2)	0	0

CPT = Child-Pugh Turcotte; DAA = direct acting antiviral; MELD = model for end stage liver disease; Peg-IFN = pegylated interferon; RBV = ribavirin; SD = standard deviation
*Total percentage may not add to 100% due to rounding.

Study Results

Table 26 presents the SVR12 for the ASTRAL-4 trial by HCV genotype. All 3 treatment groups met their primary efficacy endpoints with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%. The p-value was < 0.001 for the comparison with the SVR12 for each treatment group.

Table 26. SVR12 in Study ASTRAL-4 by HCV Genotype

	EPCLUSA 12 Weeks (N = 90) % (n/N)	EPCLUSA + RBV 12 Weeks (N = 87) % (n/N)	EPCLUSA 24 Weeks (N = 90) % (n/N)
Overall SVR12	83 (75/90)	94 (82/87)	86 (77/90)
Genotype 1	88 (60/68)	96 (65/68)	92 (65/71)
Genotype 1a	88 (44/50)	94 (51/54)	93 (51/55)
Genotype 1b	89 (16/18)	100 (14/14)	88 (14/16)
Genotype 3	50 (7/14)	85 (11/13)	50 (6/12)
Genotype 2, 4 and 6	100 (8/8)[a]	100 (6/6)[b]	86 (6/7)[c]

RBV = ribavirin

a. N=4 for genotype 2 and N=4 for genotype 4

b. N=4 for genotype 2 and N=2 for genotype 4

c. N=4 for genotype 2, N=2 for genotype 4 and N=1 for genotype 6.

Note: There were no patients enrolled with genotype 5 infection.

Table 27 presents the SVR12 for genotype 1 or 3 HCV infected patients in the ASTRAL-4 trial by prior treatment.

Table 27. SVR12 for Genotype 1 or 3 HCV Infected Patients in the ASTRAL-4 Trial by Prior Treatment

	EPCLUSA 12 Weeks		EPCLUSA + RBV 12 Weeks		EPCLUSA 24 Weeks	
	GT1 (N = 68) % (n/N)	GT3 (N = 14) % (n/N)	GT1 (N = 68) % (n/N)	GT3 (N = 13) % (n/N)	GT1 (N = 71) % (n/N)	GT3 (N = 12) % (n/N)
Treatment-naive	92 (22/24)	50 (3/6)	93 (25/27)	80 (8/10)	89 (33/37)	60 (3/5)
Treatment Experienced	86 (38/44)	50 (4/8)	98 (40/41)	100 (3/3)	94 (32/34)	43 (3/7)

Table 28 presents the virologic outcome for patients with genotype 1 or 3 HCV in the ASTRAL-4 trial. No patients with genotype 2, 4 or 6 HCV experienced virologic failure.

Table 28. Virologic Failure for Patients with Genotype 1 and 3 HCV in ASTRAL-4 Trial

	EPCLUSA 12 Weeks (N = 82) % (n/N)	EPCLUSA + RBV 12 Weeks (N = 81) % (n/N)	EPCLUSA 24 Weeks (N = 83) % (n/N)
Virologic Failure (relapse and on-treatment failure)			
Genotype 1[a]	7 (5/68)	1 (1/68)	4 (3/71)
Genotype 1a	6 (3/50)	2 (1/54)	4 (2/55)
Genotype 1b	11 (2/18)	0 (0/14)	6 (1/16)
Genotype 3	43 (6/14)	15 (2[b]/13)	42 (5[c]/12)

RBV = ribavirin

a. No patients with genotype 1 HCV had on- treatment virologic failure.

b. One patient had on-treatment virologic failure; PK data for this patient was consistent with non-adherence.

c. One patient had on-treatment virologic failure.

The overall SVR12 (virologic cure) in ASTRAL-4 for the recommended treatment regimen was 94% (82/87).

Changes in MELD and CPT score from baseline to post-treatment Week 12 (secondary endpoint) were analyzed for patients who achieved SVR12 and for whom data were available (N = 234) to assess the effect of SVR12 on hepatic function post-treatment. Of the 82 subjects treated with EPCLUSA + RBV for 12 weeks who achieved SVR12, 81 had MELD and CPT assessments at baseline and post-treatment week 12.

Change in MELD score: Among those who achieved SVR12 with 12 weeks treatment with EPCLUSA + RBV, 51% (41/81) and 15% (12/81) had an improvement or no change in MELD score from baseline to post-treatment week 12, respectively; of the 10 patients whose MELD score was ≥ 15 at baseline, 40% (4/10) had a MELD score < 15 at post-treatment Week 12. Improvement in MELD score was due to improvement (decreases) in bilirubin.

Change in CPT: Among those who achieved SVR12 with 12 weeks treatment with EPCLUSA + RBV, 41% (33/81) and 49% (40/81) had an improvement or no change of CPT scores from baseline to post-treatment week 12, respectively. Of the 72 patients who had CPT B cirrhosis at baseline, 11% (8/72) had CPT A cirrhosis at post-treatment Week 12. Improvement in CPT score was due to improvements in albumin (increases) and bilirubin (decreases).

Similar proportions of subjects treated with EPCLUSA for 12 or 24 weeks had improvements in MELD and CPT scores compared with subjects treated with EPCLUSA + RBV for 12 weeks.

MICROBIOLOGY

Antiviral Activity in Cell Culture

The EC_{50} values of sofosbuvir and velpatasvir against full-length or chimeric replicons encoding NS5B and NS5A sequences from the laboratory strains are presented in Table 29. The EC_{50} values of sofosbuvir and velpatasvir against clinical isolates are presented in Table 30.

Table 29. Activity of Sofosbuvir and Velpatasvir Against Full Length or Chimeric Laboratory Replicons

Replicon Genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]
1a	40	0.014
1b	110	0.016
2a	50	0.005-0.016[c]
2b	15[b]	0.002-0.006[c]
3a	50	0.004
4a	40	0.009
4d	NA	0.004
5a	15[b]	0.021-0.054[d]
6a	14[b]	0.006-0.009
6e	NA	0.130[d]

NA = Not available

a. Mean value from multiple experiments of same laboratory replicon.

b. Stable chimeric 1b replicons carrying NS5B genes from genotype 2b, 5a or 6a were used for testing.

c. Data from various strains of full length NS5A replicon or chimeric NS5A replicons carrying full-length NS5A gene that contains L31 or M31 polymorphisms.

d. Data from a chimeric NS5A replicon carrying NS5A amino acids 9-184.

Table 30. Activity of Sofosbuvir and Velpatasvir Against Transient Replicons Containing NS5A or NS5B from Clinical Isolates

Replicon Genotype	Replicons containing NS5B from clinical isolates		Replicons containing NS5A from clinical isolates	
	Number of clinical isolates	Median sofosbuvir EC_{50}, nM (range)	Number of clinical isolates	Median velpatasvir EC_{50}, nM (range)
1a	67	62 (29-128)	23	0.019 (0.011-0.078)
1b	29	102 (45-170)	34	0.012 (0.005-0.500)
2a	15	29 (14-81)	8	0.011 (0.006-0.364)
2b	NA	NA	16	0.002 (0.0003-0.007)
3a	106	81 (24-181)	38	0.005 (0.002-1.871)
4a	NA	NA	5	0.002 (0.001-0.004)
4d	NA	NA	10	0.007 (0.004-0.011)
4r	NA	NA	7	0.003 (0.002-0.006)
5a	NA	NA	42	0.005 (0.001-0.019)
6a	NA	NA	26	0.007 (0.0005-0.113)
6e	NA	NA	15	0.024 (0.005-0.433)

NA=Not Available

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a, and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a, and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In vitro selection of HCV replicons with reduced susceptibility to velpatasvir was performed in cell culture for multiple genotypes including 1a, 1b, 2a, 3a, 4a, 5a, and 6a. Variants were selected at NS5A resistance associated positions 24, 28, 30, 31, 32, 58, 92, and 93. The resistance associated variants (RAVs) selected in 2 or more genotypes were F28S, L31I/V, and Y93H. From site-directed mutagenesis studies, NS5A RAVs that showed a > 2.5-fold reduction in velpatasvir susceptibility are listed in Table 31 below. No individual substitutions tested in genotypes 2a, 4a, or 5a conferred a > 100-fold reduction in velpatasvir susceptibility (see **MICROBIOLOGY**, **Resistance**, **In Clinical Trials**, Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome). Combinations of these variants often showed greater reductions in susceptibility to velpatasvir than single RAVs alone.

Table 31. Phenotypic Change of Genotype 1-6 NS5A Substitutions to Velpatasvir

Genotype	> 2.5-100-fold*	> 100-fold*
1a	M28A/T, Q30E/G/K, L31F/I/M/V, P32L, H58D, Y93C/L/S/T	M28G, A92K, Y93H/N/R/W
1b	Q24K, L31F/I, P58T, Y93H/N/T	A92K
2a	F28S, L31V, C92R, Y93H/N	None
2b	L28F, P58A, C92S, Y93F	C92T, Y93H/N
3a	A30H/K, L31F/M, P58G	Y93H
4a	L28T, Y93H/N/S	None
5a	L31I	None
6a	F28M/V, L31I/M, T58G/H, A92T, T93A/H/N/S	L31V, P32A/L/Q/R

*Fold change was calculated as the ratio of mutant EC_{50} to wild-type EC_{50}.

In Clinical Trials

Studies in Patients with Compensated Liver Disease

In a pooled analysis of patients without cirrhosis or with compensated cirrhosis who received EPCLUSA for 12 weeks in Phase 3 trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3), 12 patients (2 with genotype 1 and 10 with genotype 3) qualified for resistance analysis due to virologic failure. One additional virologic failure patient with genotype 3 HCV infection at baseline was reinfected with genotype 1a HCV at virologic failure and was excluded from the virological analysis. No patients with genotype 2, 4, 5, or 6 HCV infection experienced virologic failure.

Of the two genotype 1 virologic failure patients, one patient had virus with emergent NS5A RAV Y93N and the other patient had virus with emergent NSA RAVs L31I/V and Y93H at virologic failure. Both patients had virus at baseline harboring NS5A RAVs. No NS5B nucleoside inhibitor (NI) RAVs were observed at failure in the two patients.

Of the ten genotype 3 virologic failure patients, Y93H was observed in all 10 patients at failure (6 had Y93H emerge post-treatment and 4 patients had Y93H at baseline and post-treatment). No NS5B NI RAVs were observed at failure in the ten patients.

Studies in Patients with Decompensated Cirrhosis

In the ASTRAL-4 trial in patients with decompensated cirrhosis who received EPCLUSA + RBV for 12 weeks, 3 patients (one with genotype 1 and two with genotype 3) qualified for resistance analysis due to virologic failure. No patients with genotype 2 or 4 HCV infection in the EPCLUSA + RBV 12 Weeks group experienced virologic failure.

The one virologic failure patient with genotype 1 HCV had no NS5A or NS5B RAVs at failure.

Of the two genotype 3 virologic failure patients, one had NS5A RAV Y93H emerge at failure. Another patient had virus with Y93H at baseline and virologic failure and also developed low levels (< 5%) of NS5B NI RAVs N142T and E237G at failure. Pharmacokinetic data of this patient was consistent with non-adherence.

In the ASTRAL-4 trial, two patients treated with EPCLUSA for 12 or 24 weeks without ribavirin had emergent NS5B S282T at low levels (< 5%) along with L159F.

Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome

Studies in Patients with Compensated Liver Disease

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients without cirrhosis or with compensated cirrhosis (ASTRAL-1, ASTRAL-2, and ASTRAL-3). Of the 1035 patients treated with EPCLUSA in the ASTRAL-1, ASTRAL-2, and ASTRAL-3 studies, 1023 patients were included in the analysis of NS5A RAVs; 7 subjects were excluded as they neither achieved SVR12 nor had virologic failure and 5 additional patients were excluded as NS5A gene sequencing failed. In the pooled analysis of the Phase 3 trials, 380/1023 (37%) patients' virus had baseline NS5A RAVs. Genotype 2, 4, and 6 HCV infected patients had a higher prevalence of NS5A RAVs (70%, 63% and 52%, respectively) compared to genotype 1 (23%), genotype 3 (16%), and genotype 5 (18%) HCV infected patients.

SVR12 in patients with or without baseline NS5A RVAs in ASTRAL-1, ASTRAL-2, and ASTRAL-3 trials is shown in Table 32.

Table 32. SVR12 in Patients with or without Baseline NS5A RAVs by HCV Genotype (ASTRAL-1, ASTRAL-2, ASTRAL-3)

	EPCLUSA 12 Weeks			
SVR12	Genotype 1	Genotype 3	Genotype 2, 4, 5 or 6	Total
With any baseline NS5A RAVs	97% (73/75)	88% (38/43)	100% (262/262)	98% (373/380)
Without baseline NS5A RAVs	100% (251/251)	97% (225/231)	100% (161/161)	99% (637/643)

RAVs = resistance associated variants; RBV = ribavirin; SVR = sustained virologic response

Among the 75 genotype 1 patients who had baseline NS5A RAVs, SVR12 was 97% (67/69) and 100% (6/6) in patients with baseline NS5A RAVS that confer ≤ 100-fold and > 100-fold reduced susceptibility to velpatasvir, respectively. Among the 43 genotype 3 patients who had baseline

NS5A RAVs, SVR12 was 94% (15/16) and 85% (23/27) in patients with NS5A RAVS that confer ≤ 100-fold and > 100-fold reduced susceptibility to velpatasvir, respectively. The four genotype 3 patients who had baseline NS5A RAVs conferring >100-fold reduced susceptibility to velpatasvir and failed to achieve SVR12 all had NS5A substitution Y93H at baseline. Twenty-one of 25 genotype 3 patients with baseline NS5A substitution Y93H achieved SVR12.

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 trials. SVR12 was achieved in all 77 patients who had baseline NS5B NI RAVs including N142T, L159F, E/N237G, C/M289L/I, L320F/I/V, V321A/I, and S282G+V321I.

Studies in Patients with Decompensated Cirrhosis

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients with decompensated cirrhosis (ASTRAL-4). Of the 87 patients treated with EPCLUSA + RBV in the ASTRAL-4 study, 85 patients were included in the analysis of NS5A RAVs; 2 patients were excluded as they neither achieved SVR12 nor had virologic failure. Among the patients who received treatment with EPCLUSA + RBV for 12 weeks, 29% (25/85) of patients had baseline virus with NS5A RAVs [29% (19/66), 75% (3/4), 15% (2/13), and 50% (1/2) for patients with genotype 1, 2, 3 and 4 HCV, respectively].

SVR12 in patients with or without baseline NS5A RAVs in the EPCLUSA + RBV 12 week group of ASTRAL-4 trial is shown in Table 33.

Table 33. SVR12 in Patients with or without Baseline NS5A RAVs by HCV Genotype (ASTRAL-4)

	EPCLUSA + RBV 12 Weeks			
	Genotype 1	Genotype 3	Genotype 2 or 4	Total
With any baseline NS5A RAVs	100% (19/19)	50% (1/2)	100% (4/4)	96% (24/25)
Without baseline NS5A RAVs	98% (46/47)	91% (10/11)	100% (2/2)	98% (58/60)

RAVs = resistance associated variants; RBV = ribavirin

The single genotype 3 patient who had baseline NS5A RAVs and failed to achieve SVR12 had NS5A substitution Y93H at baseline and the pharmacokinetic data of this patient was consistent with non-adherence.

Three patients in the EPCLUSA + RBV 12 week group had baseline NS5B NI RAVs (N142T and L159F) and all three patients achieved SVR12.

Cross Resistance

Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors. *In vitro* data suggests that the majority of NS5A RAVs that confer resistance to ledipasvir and daclatasvir remained susceptible to velpatasvir. Velpatasvir was fully active against the sofosbuvir resistance-associated substitution S282T in NS5B while all velpatasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Both sofosbuvir and velpatasvir were fully active against substitutions associated with resistance to other classes of direct acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. The efficacy of EPCLUSA has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

TOXICOLOGY

Repeat-Dose Toxicity

Sofosbuvir

Sofosbuvir or GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer, was evaluated in repeat-dose oral toxicity studies up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The primary sofosbuvir target organs identified were the gastrointestinal (GI) and hematopoietic (erythroid) systems. In a 7-day toxicity dog study with GS-9851, a dose of 1500 mg/kg/day resulted in (but were not limited to) increased mucus secretions in the stomach, glycogen depletion, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, with associated histopathologic liver findings and increased QT/QTc intervals in dogs. At the adverse dose, GS-331007 exposure levels in the dog study were at least 63-fold higher than HCV-infected subjects treated once daily with EPCLUSA. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), sofosbuvir effects included (but were not limited to) GI-related clinical signs (e.g., soft feces and emesis) and a decrease (e.g., approximately 10%) in mean red cell indices that were observed mainly in the high-dose group of dogs. One male dog was euthanized moribund with intestinal hemorrhage. The relationship to sofosbuvir was undetermined. In general, exposure levels in the chronic toxicity studies at the no observed adverse effect level were at least 5-fold (based on AUC of GS-331007) higher than HCV-infected subjects treated once daily with EPCLUSA.

Velpatasvir

Velpatasvir was well tolerated in studies for up to 4 weeks in the mouse, 26 weeks in the rat, and 39 weeks in the dog. No target organs were identified at the highest dose evaluated in each respective repeat dose toxicity study, corresponding to exposure margins of 74-, 5-, and 10-fold greater in mice, rats, and dogs, respectively, than those in HCV-infected subjects treated once daily with EPCLUSA.

Genotoxicity and Carcinogenicity

Sofosbuvir

Sofosbuvir, when administered as the diastereomeric mixture GS-9851, was not genotoxic in a bacterial mutagenicity assay, in an *in vitro* chromosome aberration test using human peripheral blood lymphocytes and in an *in vivo* mouse micronucleus assay.

Sofosbuvir was not carcinogenic in the 2-year mouse and rat carcinogenicity studies at doses resulting in GS-331007 exposures up to 15-times in mice and 9-times in rats, higher than human exposure at 400 mg dose.

Velpatasvir

Velpatasvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rat micronucleus assays.

Carcinogenicity studies with velpatasvir are ongoing.

Fertility

Sofosbuvir

Sofosbuvir had no effects on fertility when evaluated in rats at exposures (AUC) to the predominant circulating metabolite GS-331007 of at least 4-fold the exposure in humans at the recommended clinical dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through lactation day 20 at daily GS-331007 exposures of approximately 6-fold higher than human exposures at the recommended clinical dose.

Velpatasvir

Velpatasvir had no adverse effects on fertility in rats at AUC exposure 6-fold higher than the human exposure at the recommended clinical dose.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrEPCLUSA™
sofosbuvir and velpatasvir tablets

Read this carefully before you start taking **Epclusa**. Read it again every time you get a refill. This leaflet is a summary. It will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment. Ask whether there is any new information about **Epclusa**.

What is Epclusa used for?
- **Epclusa** treats chronic (lasting longer than 6 months) hepatitis C infection in adults.
- Your doctor may decide to prescribe **Epclusa** in combination with ribavirin.
- **Epclusa** cures chronic hepatitis C in most patients. Cure means that there is no virus left in the body. This is confirmed with a blood test 3 months after the end of treatment.
- Do NOT give to children under 18 years of age. It is not known if **Epclusa** is safe or works in children.

How does Epclusa work?
Epclusa contains two medicines, sofosbuvir and velpatasvir, that have been combined together into one tablet (pill). This type of treatment course (regimen) is also known as a single tablet regimen. It provides a complete treatment for hepatitis C. For most patients, **Epclusa** does not need to be taken with ribavirin.

- Sofosbuvir and velpatasvir block the virus from making additional copies of itself. They work together to help prevent viral growth, thereby reducing the infection and allowing the body to clear (remove) the virus from the blood and liver.
- Curing chronic hepatitis C virus can help reduce the risk of illness and death caused by liver disease.

What are the ingredients in Epclusa?
Medicinal ingredients: Sofosbuvir, Velpatasvir
Non-medicinal ingredients: Copovidone, croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The coating of the tablets contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

Epclusa comes in the following dosage forms:
Epclusa comes in tablets. Each tablet contains sofosbuvir (400 milligrams) and velpatasvir (100 milligrams). **Epclusa** tablets are pink. They have a diamond shape. The tablets say “GSI” on one side and “7916” on the other side. Each bottle contains 28 tablets. The bottle has a cap that children cannot open. The bottle also contains some polyester coil (which looks white and fluffy). Do NOT eat the coil. It is meant to keep your medicine fresh.

Do not use Epclusa if:

- You are allergic to velpatasvir, sofosbuvir (also called **Sovaldi**® when it is used with other medicines without velpatasvir or ledipasvir), or any of the other ingredients in this product. (Read also "**What are the ingredients in Epclusa?**" above.)
- You are taking **Epclusa** in combination with ribavirin and you are pregnant or may become pregnant or if you are a man whose female partner(s) is (are) pregnant or may become pregnant.

To help avoid side effects and ensure you take your medicine properly, talk to your doctor before you take Epclusa. Talk about any health conditions or problems you may have, including if you:

- have liver problems other than hepatitis C infection.
- have had a recent liver transplant.
- have hepatitis B.
- have HIV.
- have severe kidney disease or you are on dialysis.
- are breastfeeding or plan to breastfeed. Do NOT breastfeed while taking **Epclusa**.
- are taking anything listed in the section "**The following may interact with Epclusa**".

- Your doctor may monitor your liver function during **Epclusa** treatment, under some conditions.

Pregnancy:

- If you are pregnant or plan to become pregnant, ask your doctor for advice before taking this medicine. It is NOT known if **Epclusa** can harm your unborn child.
- You or your partner must not become pregnant while taking **Epclusa** in combination with ribavirin or become pregnant within 6 months after you have stopped taking ribavirin. Ribavirin may cause birth defects and death of the fetus. Extreme care must be taken to avoid becoming pregnant.
- Your doctor will order monthly pregnancy test during treatment with **Epclusa** in combination with ribavirin and for 6 months after treatment has stopped.
- If you or your partner become pregnant while taking **Epclusa** in combination with ribavirin, contact your doctor. Read the package insert for ribavirin for information regarding pregnancy.

Contraception:

- If you are taking **Epclusa** in combination with ribavirin, then you and your partner must use 2 effective methods of birth control during the entire treatment and for 6 months after you stop taking this combination.

Another warning you should know about:
Because **Epclusa** already contains sofosbuvir, do not take **Epclusa** with any other medicines containing sofosbuvir (e.g. **Sovaldi**, **Harvoni**®).

Tell your doctor or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Epclusa:

- amiodarone (Cordarone®), a drug used to treat certain abnormal heart rhythms. Amiodarone may slow your heartbeat. Get medical help right away if you get symptoms such as fainting, dizziness, lightheadedness, weakness, shortness of breath.
- carbamazepine (Tegretol®), a drug used to treat seizures, nerve pain, and bipolar disorder.
- digoxin (Lanoxin®, Toloxin®), a drug used to treat congestive heart failure and a certain abnormal heart rhythm (atrial fibrillation).
- efavirenz (Sustiva®, **Atripla**®), a drug used to treat HIV.
- medicines for indigestion, heartburn, or ulcers. Examples are nizatidine (Axid®), famotidine (Pepcid AC®, Peptic Guard®, Ulcidine®), cimetidine (Tagamet®), ranitidine (Zantac®), esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Losec®), rabeprazole (Aciphex®) and pantoprazole (Pantoloc®) or antacids (like Tums®, Rolaids® or Alka-Seltzer®) that have an ingredient to protect the stomach.
- oxcarbazepine (Trileptal®), a drug used to control seizures.
- phenobarbital, a drug used to treat anxiety and to control seizures.
- phenytoin (Dilantin®), a drug used to control seizures.
- rifabutin (Mycobutin®), a drug used to treat tuberculosis.
- rifampin (Rifadin®, Rifater®, Rofact®), a drug used to treat tuberculosis.
- rosuvastatin (Crestor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- St. John's wort (*Hypericum perforatum*), an herbal product used for anxiety or depression.
- tipranavir (Aptivus®) or tipranavir/ritonavir (Aptivus® and Norvir®), drugs used to treat HIV.
- tenofovir disoproxil fumarate (**Atripla**, **Complera**®, **Stribild**®, **Truvada**®, **Viread**®), to treat HIV.

How to take Epclusa:

- Take this medicine with or without food.
- This medicine is taken for 12 weeks.
- If you are taking an antacid, you may need to take **Epclusa** at a different time than the antacid. Talk to your doctor or pharmacist.
- Do NOT stop taking **Epclusa** without first talking with your doctor.

Usual adult dose:

- Take one tablet once each day.

Overdose:

If you think you have taken too much **Epclusa**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

It is important to take **Epclusa** each day.

- **If you miss a dose** of **Epclusa** and you notice within 18 hours, take a tablet as soon as you can. Then take the next dose at your usual time.
- **If you miss a dose** of **Epclusa** and you notice after 18 hours, wait and take the next dose at your usual time. Do NOT take a double dose (two doses close together).

What to do if you vomit (throw up):

- If you vomit **less than 3 hours** after taking **Epclusa**, take another tablet.
- If you vomit **more than 3 hours** after taking **Epclusa**, wait. Do NOT take another tablet until you are scheduled to take the next tablet.

What are possible side effects from using Epclusa?
The most common side effects of **Epclusa** are tiredness and headache.

These are not all the possible side effects you may feel when taking **Epclusa**. If you experience any side effects not listed here, contact your doctor.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your doctor.

Reporting side effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store **Epclusa** below 30 ^{o}C (86 ^{o}F).
- Keep **Epclusa** in its original container.
- Do NOT use **Epclusa** if the seal over the bottle opening is broken or missing.
- Keep this medication where children cannot reach it or see it.

If you want more information about Epclusa:

- Talk to your doctor or pharmacist.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.gilead.ca), or by calling 1-800-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

Last Revised: July 8, 2016

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Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

e186388-GS-000

THE ATTACHED IS EXHIBIT "I" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 13TH DAY OF OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

Product Monograph

INCLUDING PATIENT MEDICATION INFORMATION

PrVOSEVI™

(sofosbuvir/velpatasvir/voxilaprevir) tablets

400 mg/100 mg/100 mg

Antiviral Agent

Gilead Sciences Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3
Canada

www.gilead.ca

Date of Preparation:
August 16, 2017

Submission Control No.: 202324

TABLE OF CONTENTS

VOSEVI™
sofosbuvir/velpatasvir/voxilaprevir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 400 mg sofosbuvir 100 mg velpatasvir 100 mg voxilaprevir	lactose monohydrate

*For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adult patients, without cirrhosis or with compensated cirrhosis, who have:

- genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor;
- genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

Geriatrics (≥ 65 years of age)

The response rates observed for patients 65 years of age and over were similar to those of younger patients across treatment groups. VOSEVI can be administered in geriatric patients (see **ACTION AND CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS**).

Pediatrics (< 18 years of age)

Safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

VOSEVI is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Table 1 lists drugs which are contraindicated with VOSEVI (see **DRUG INTERACTIONS**).

Table 1 Drugs that are Contraindicated with VOSEVI

Drug Class: Drug Name	Effect on Concentration	Mechanism of Action	Clinical Comment
Anticoagulants: dabigatran etexilate	↑ dabigatran	P-gp inhibition	Increased risk of bleeding.
Anticonvulsants: phenobarbital, phenytoin	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Induction of P-gp and CYP450	Risk of loss of therapeutic effect of VOSEVI.
Antimycobacterials: rifampin	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Induction of P-gp and CYPs	Risk of loss of therapeutic effect of VOSEVI.
Herbal products: St. John's wort (*Hypericum perforatum*)	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Induction of P-gp and CYP450	Risk of loss of therapeutic effect of VOSEVI.
HMG-CoA reductase inhibitors: rosuvastatin	↑ rosuvastatin	BCRP and OATP1B inhibition	Increased risk of statin-related myopathy, including rhabdomyolysis.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Potential for Hepatitis B Virus (HBV) Reactivation**

Screen all patients for evidence of current or prior HBV infection before initiating VOSEVI treatment. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct-acting antivirals (DAAs) in patients co-infected with HBV (see **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**).

General

Treatment with VOSEVI should be initiated and monitored by a physician experienced in the management of chronic HCV infection.

Data to support the treatment of patients infected with HCV genotype 5 or genotype 6 who have failed prior therapy of an HCV regimen containing an NS5A inhibitor are limited. The indication for treatment of these patients is based on extrapolation of relevant clinical and *in vitro* data (see **CLINICAL TRIALS** and **MICROBIOLOGY**).

No clinical data are available to support the treatment of HCV patients with genotype 5 or genotype 6 infection who have failed prior therapy of an HCV regimen containing sofosbuvir without an NS5A inhibitor (see **CLINICAL TRIALS**).

VOSEVI should not be administered concurrently with other medicinal products containing sofosbuvir.

Use with Potent P-gp Inducers and/or Moderate to Potent Inducers of CYP

Medicinal products that are potent inducers of P-glycoprotein (P-gp) and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 [e.g., St. John's wort (*Hypericum perforatum*), and carbamazepine] may significantly decrease plasma concentrations of sofosbuvir, velpatasvir, or voxilaprevir leading to reduced therapeutic effect of VOSEVI and potential loss of virologic response. These agents should not be used with VOSEVI (see **DRUG INTERACTIONS**).

Cardiovascular

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with daclatasvir or simeprevir. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen (HARVONI® [ledipasvir/sofosbuvir]). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with VOSEVI is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered VOSEVI:

- Counsel patients about the risk of symptomatic bradycardia.
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking VOSEVI who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting VOSEVI should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

Potential for Hepatitis B Virus Reactivation

Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV co-infected patients who were undergoing, or completed treatment with DAAs. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patients with serologic evidence of resolved HBV infection (ie, HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

Hepatic

VOSEVI is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to significant increases in the exposures of voxilaprevir in these patients (AUC ↑ 299% and 500% in HCV-negative patients with moderate and severe hepatic impairment, respectively); the safety and efficacy of VOSEVI have not been established in HCV-infected patients with moderate or severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Gastrointestinal

VOSEVI contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption).

Renal

The safety and efficacy of VOSEVI have not been established in patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] < 30 mL/min) or end stage renal disease (ESRD) requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY**).

Sexual Function/Reproduction

There are no data on the effect of sofosbuvir, velpatasvir, or voxilaprevir on human fertility. No effects on fertility were observed in animal studies for sofosbuvir, velpatasvir or voxilaprevir (see **TOXICOLOGY**).

Special Populations

Pregnant Women

Pregnancy should be avoided while taking VOSEVI as there are no data on the use of VOSEVI in pregnant women. VOSEVI should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their healthcare provider immediately in the event of a pregnancy.

No effects on pre- or post-natal development were observed in animal reproduction studies at the highest doses of sofosbuvir tested. In the rat and rabbit embryo fetal studies, and the rat pre/post-natal study, exposure to the predominant circulating metabolite GS-331007 at the highest dose was approximately 6-fold, 16-fold, and 7-fold the exposure in humans at the recommended clinical dose, respectively.

No effects on pre- or post-natal development have been observed in animal reproduction studies at the highest doses of velpatasvir tested. In the mouse, rat, and rabbit embryo fetal studies, and rat pre/post-natal study velpatasvir exposure was approximately 23-fold, 4-fold, 0.5-fold, and 3-fold the exposure in humans at the recommended clinical dose, respectively.

No effects on pre- or post-natal development have been observed in animal reproduction studies at the highest doses of voxilaprevir tested. In the rat and rabbit embryo fetal studies, and rat pre/post-natal study voxilaprevir exposure was approximately 141-fold, 4-fold, and 238-fold the exposure in humans at the recommended clinical dose, respectively.

Nursing Women

It is not known whether sofosbuvir, metabolites of sofosbuvir, velpatasvir, or voxilaprevir are excreted in human breast milk. The sofosbuvir predominant circulating metabolite GS-331007 and velpatasvir are present in the milk of lactating rats; they had no clear effect on nursing pups. When administered to lactating rats, voxilaprevir was detected in the plasma of nursing pups. Because a risk to the newborn/infant cannot be excluded, mothers should be instructed not to breastfeed if they are taking VOSEVI.

Pediatrics (< 18 years of age)

The safety and efficacy of VOSEVI in pediatric patients have not been established.

Geriatrics (≥ 65 years of age)

The response rates observed for patients 65 years of age and over were similar to those of patients < 65 years of age across treatment groups.

Pre-and Post-Liver Transplant Patients

The safety and efficacy of VOSEVI have not been established in patients awaiting liver transplantation or in patients with recurrent HCV infection post-liver transplant.

HCV/HIV Co-infection

The safety and efficacy of VOSEVI have not been established in HCV patients co-infected with Human Immunodeficiency Virus (HIV).

VOSEVI has been shown to increase tenofovir exposure when used together with an HIV regimen containing tenofovir disoproxil fumarate (tenofovir DF). Patients receiving VOSEVI concomitantly with tenofovir DF, particularly those at increased risk for renal dysfunction,

should be monitored for tenofovir-associated adverse reactions. Refer to Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.

Efavirenz has been shown to significantly decrease the concentration of velpatasvir and is expected to decrease the concentration of voxilaprevir; therefore co-administration of VOSEVI with an efavirenz-containing regimen is not recommended (see **DRUG INTERACTIONS**).

HCV/HBV Co-infection

The safety and efficacy of VOSEVI have not been established in HCV patients co-infected with HBV. HBV reactivation has been reported during treatment and post-treatment with DAAs in patients co-infected with HBV who were not undergoing treatment for HBV infection (see **WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

Monitoring and Laboratory Tests

If VOSEVI is administered with amiodarone, close monitoring for bradycardia is recommended (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**). Refer to the amiodarone Product Monograph.

Clearance of HCV may lead to increased replication of HBV in patients who are co-infected with HCV and HBV. Co-infected patients should be monitored for clinical and laboratory signs (eg, HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

Patients Treated with Vitamin K Antagonists

As liver function may improve during treatment with VOSEVI, a close monitoring of International Normalised Ratio (INR) values is recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety profile of VOSEVI was established in patients infected with HCV, without cirrhosis or with compensated cirrhosis.

Adverse reactions data for VOSEVI were derived from two Phase 3 clinical trials (POLARIS-1 and POLARIS-4) that evaluated a total of 445 patients with chronic HCV infection, without cirrhosis or with compensated cirrhosis, who received VOSEVI for 12 weeks (see **CLINICAL TRIALS**).

The proportion of patients who permanently discontinued treatment due to adverse events was 0.2% for patients receiving VOSEVI for 12 weeks. Of the 445 patients, 2% had at least one serious adverse event (SAE), with no patients experiencing a treatment-related SAE.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions (adverse events assessed as causally related by the investigator), all grades, observed in ≥ 10% of patients receiving 12 weeks of treatment with VOSEVI in clinical trials include headache (22%), fatigue (18%), diarrhea (13%), and nausea (12%). Of patients receiving VOSEVI who experienced these adverse reactions, 76% of subjects had an adverse reaction of mild (Grade 1) severity.

The adverse reactions (Grades 2 to 4) observed in ≥ 1% of patients receiving 12 weeks of treatment with VOSEVI in clinical trials are listed in Table 2.

Table 2. Adverse Reactions (Grades 2-4) Reported in ≥ 1% of Patients Receiving 12 Weeks of VOSEVI[a] from the Phase 3 Studies (POLARIS-1, POLARIS-4)

	POLARIS-1		POLARIS-4	
	VOSEVI 12 weeks N = 263	**Placebo 12 weeks N = 152**	**VOSEVI 12 weeks N = 182**	**SOF/VEL 12 weeks N = 151**
Headache	5%	2%	4%	2%
Fatigue	3%	4%	2%	7%
Diarrhea	1%	2%	2%	0
Insomnia	2%	<1%	1%	0
Asthenia	1%	<1%	2%	<1%

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Adverse reactions (Grades 2 to 4) occurring in less than 1% of patients receiving 12 weeks of treatment with VOSEVI in clinical trials are listed below in Table 3 by body system.

Table 3. Adverse Reactions (Grades 2-4) Reported in < 1% of Patients Receiving 12 Weeks of VOSEVI[a] from the Pooled Phase 3 Studies (POLARIS-1, POLARIS-4)

Body System	**VOSEVI 12 Weeks**
Gastrointestinal Disorders	Abdominal discomfort, abdominal pain, abdominal pain upper, eructation, flatulence, functional gastrointestinal disorder, gastroesophageal reflux disease, nausea
General Disorders and Administration Site Conditions	Chills, energy increased, influenza like illness, thirst
Infections and Infestations	Subcutaneous abscess

Body System	VOSEVI 12 Weeks
Injury, Poisoning and Procedural Complications	Ligament sprain
Metabolism and Nutrition Disorders	Decreased appetite, gout
Musculoskeletal and Connective Tissue Disorders	Arthralgia, myalgia, polyarthritis
Nervous System Disorders	Disturbance in attention, dizziness, dizziness postural, migraine, somnolence
Respiratory, Thoracic and Mediastinal Disorders	Cough, rhinorrhea
Skin and Subcutaneous Tissue Disorders	Dry skin, night sweats, pruritus, rash maculo-papular, vitiligo
Vascular Disorders	Hot flush

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

For information on the safety profile of sofosbuvir in combination with velpatasvir, consult the EPCLUSA Product Monograph.

Abnormal Hematologic and Clinical Chemistry Findings

The frequency of treatment-emergent laboratory abnormalities (Grades 2 to 4) occurring in at least 1% of patients receiving 12 weeks of treatment with VOSEVI are described in Table 4.

Table 4. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 1% of Patients Receiving 12 Weeks of VOSEVI from the Phase 3 Studies (POLARIS-1, POLARIS-4)

Laboratory Abnormality Parameters	POLARIS-1		POLARIS-4	
	VOSEVI 12 weeks N = 263	Placebo 12 weeks N = 152	VOSEVI 12 weeks N = 182	SOF/VEL 12 weeks N = 151
Chemistry				
ALT (> 2.5 x ULN)	<1%	5%	2%	0%
AST (> 2.5 x ULN)	<1%	9%	2%	0%
Creatine Kinase (≥ 6 x ULN)	2%	2%	2%	1%
Hyperbilirubinemia (> 1.5 x ULN)	3%	3%	3%	1%
Hyperglycemia (> 8.91 mmol/L)	11%	16%	15%	15%
Lipase (> 1.5 x ULN)	7%	5%	10%	4%
Hematology				

Lymphocytes (< 600/mm^3)	<1%	3%	2%	<1%
Neutrophils (< 1000/ mm^3)	1%	<1%	1%	2%
Platelets (< 100 x 10^9/L)	6%	6%	5%	6%

ULN = Upper Limit of Normal

Total bilirubin

In the Phase 3 trials, increases in total bilirubin less than or equal to 1.5 × ULN were observed in 4% of patients without cirrhosis and 10% of patients with compensated cirrhosis, due to inhibition of OATP1B1 and OATP1B3 by voxilaprevir. Total bilirubin levels decreased after completing VOSEVI treatment. No patients experienced jaundice.

Post-Market Adverse Drug Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions have been identified during postapproval use of sofosbuvir-containing regimens. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Serious symptomatic bradycardia when amiodarone is coadministered with sofosbuvir in combination with another HCV DAA (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **DRUG INTERACTIONS**).

Skin and Subcutaneous Tissue Disorders

Skin rashes (sometimes with blisters or angioedema-like swelling) and angioedema.

DRUG INTERACTIONS

Overview

As VOSEVI contains sofosbuvir, velpatasvir, and voxilaprevir, any interactions that have been identified with these agents individually may occur with VOSEVI.

After oral administration of VOSEVI, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. In clinical pharmacology studies, both sofosbuvir and the primary circulating metabolite GS-331007 (dephosphorylated nucleotide metabolite) were monitored for purposes of pharmacokinetic analyses.

Drug-Drug Interactions

Potential for VOSEVI to Affect Other Drugs

Sofosbuvir and GS-331007 are not relevant inhibitors of efflux drug transporters P-gp, BCRP, renal efflux transporter MRP2, hepatic efflux transporter BSEP, hepatic uptake transporters OATP1B1, OATP1B3, OCT1, and GS-331007 is not an inhibitor of renal uptake transporters OAT1, OCT2 and renal efflux transporter MATE1. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1, and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant concentrations, velpatasvir is not an inhibitor of hepatic transporters OATP1A2 or OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

Voxilaprevir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1 and OATP1B3, and its involvement in drugs interactions with these transporters is primarily limited to the process of absorption. Coadministration of VOSEVI with drugs that are substrates of these transporters may alter the exposure of such drugs. At clinically relevant concentrations, voxilaprevir is not an inhibitor of hepatic transporter OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

Potential for Other Drugs to Affect VOSEVI

Sofosbuvir, velpatasvir, and voxilaprevir are substrates of efflux drug transporters P-gp and BCRP while GS-331007 is not. GS-331007 is not a substrate for renal transporters including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2. Voxilaprevir, and to a lesser extent velpatasvir, are also substrates of OATP1B1 and OATP1B3. *In vitro*, slow metabolic turnover of velpatasvir primarily by CYP2B6, CYP2C8, and CYP3A4 and of voxilaprevir primarily by CYP3A4 was observed.

Drugs that are potent inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., St. John's wort or carbamazepine) may significantly decrease plasma concentrations of sofosbuvir, velpatasvir, and/or voxilaprevir leading to reduced therapeutic effect of VOSEVI. Coadministration of VOSEVI with phenobarbital, phenytoin, rifampin and St. John's wort are contraindicated and coadministration with carbamazepine is not recommended (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir, velpatasvir, and/or voxilaprevir plasma concentrations without increasing GS-331007 plasma concentration. Coadministration with drugs that inhibit OATP may increase voxilaprevir plasma concentrations. Drugs that inhibit CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir and/or voxilaprevir. VOSEVI may be coadministered with P-gp, BCRP, and CYP inhibitors. The use of potent inhibitors of OATP with VOSEVI is not recommended.

Table 5 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either VOSEVI, the components of VOSEVI (sofosbuvir, velpatasvir, and voxilaprevir) as individual agents, or are predicted drug interactions that may occur with VOSEVI. The table is not all-inclusive (see **ACTION AND CLINICAL PHARMACOLOGY**).

Table 5. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Acid Reducing Agents:		
	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		It is recommended to separate antacid and VOSEVI administration by 4 hours.
H_2-receptor antagonists (e.g., famotidine)[c]		H_2-receptor antagonists may be administered simultaneously with or staggered from VOSEVI at a dose that does not exceed doses comparable with famotidine 40 mg twice daily.
Proton-pump inhibitors (e.g., omeprazole)[c]		Proton-pump inhibitor doses comparable with omeprazole 20 mg can be administered with VOSEVI.
Antiarrhythmics:		
amiodarone	Effect on amiodarone, sofosbuvir, velpatasvir, and voxilaprevir concentrations unknown	Coadministration of amiodarone with VOSEVI may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with VOSEVI is not recommended; if coadministration is required, cardiac monitoring is recommended (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).
digoxin[c]	↑ digoxin	Coadministration of VOSEVI with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with VOSEVI.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Anticoagulants:		
dabigatran etexilate[c]	↑ dabigatran	Coadministration of VOSEVI with dabigatran etexilate is contraindicated. Coadministration of VOSEVI with dabigatran etexilate may increase the concentration of dabigatran which may increase the risk of bleeding.
vitamin K antagonists	vitamin K antagonist ↔	As liver function may improve during treatment with VOSEVI, a close monitoring of INR values is recommended.
Anticonvulsants:		
carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration of VOSEVI with phenytoin or phenobarbital is contraindicated. Coadministration of VOSEVI with carbamazepine or oxcarbazepine is not recommended. Coadministration of these anticonvulsants with VOSEVI may significantly decrease the concentration of sofosbuvir, velpatasvir and voxilaprevir, and may lead to loss of therapeutic effect of VOSEVI.
Antimycobacterials:		
rifabutin rifampin[c] rifapentine*	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration of VOSEVI with rifampin is contraindicated. Coadministration of VOSEVI with rifabutin or rifapentine is not recommended. Coadministration of these antimicrobials with VOSEVI may significantly decrease the concentrations of sofosbuvir, velpatasvir and voxilaprevir, and may lead to loss of therapeutic effect of VOSEVI.
Antiretrovirals:		
atazanavir[c] lopinavir	↑ voxilaprevir	Coadministration of VOSEVI with atazanavir- or lopinavir-containing regimens is not recommended. Coadministration of these antiretrovirals with VOSEVI has been shown to substantially increase the plasma concentration of voxilaprevir, the safety of which has not been established.
efavirenz[c]	↓ velpatasvir ↓ voxilaprevir	Coadministration of VOSEVI with efavirenz-containing regimens is not recommended. Coadministration of efavirenz with VOSEVI may significantly decrease the concentrations of velpatasvir and voxilaprevir, and may lead to loss of therapeutic effect of VOSEVI.
tenofovir disoproxil fumarate (tenofovir DF)[c]	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving VOSEVI concomitantly with a regimen containing tenofovir DF. Refer to the Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
HMG-CoA Reductase Inhibitors:		
atorvastatin	↑ atorvastatin	Coadministration of VOSEVI with atorvastatin may increase the concentration of atorvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Atorvastatin may be administered with VOSEVI at a dose that does not exceed atorvastatin 10 mg. Monitoring for signs and symptoms of myopathy, including rhabdomyolysis, during concomitant use of atorvastatin with VOSEVI may be warranted.
fluvastatin lovastatin simvastatin	↑ fluvastatin ↑ lovastatin ↑ simvastatin	Coadministration of VOSEVI with fluvastatin, lovastatin, and simvastatin may increase the concentrations of these statins which is associated with increased risk of myopathy, including rhabdomyolysis. Use the lowest approved statin dose. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment. Monitoring for signs and symptoms of myopathy, including rhabdomyolysis, during concomitant use of statins with VOSEVI may be warranted.
pravastatin[c]	↑ pravastatin	Coadministration of VOSEVI with pravastatin has been shown to increase the concentration of pravastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Pravastatin may be administered with VOSEVI at a dose that does not exceed pravastatin 40 mg. Monitoring for signs and symptoms of myopathy, including rhabdomyolysis, during concomitant use of pravastatin with VOSEVI may be warranted.
rosuvastatin[c]	↑ rosuvastatin	Coadministration of VOSEVI with rosuvastatin is contraindicated. Coadministration of VOSEVI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis.
Immunosuppressants:		
cyclosporine[c]	↑ voxilaprevir	Coadministration of VOSEVI with cyclosporine is not recommended. Coadministration of voxilaprevir with cyclosporine has been shown to substantially increase the plasma concentration of voxilaprevir, the safety of which has not been established.
Oral Contraceptives:		
ethinyl estradiol-containing drugs	↔	Coadministration of VOSEVI with ethinyl estradiol-containing drugs may increase the risk of ALT elevation. Monitoring of ALT may be considered.

*Drug not marketed in Canada

a. This table is not all inclusive.

b. ↑ = increase, ↓ = decrease, ↔ = no effect.
c These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with VOSEVI

Based on drug interaction studies conducted with the components of VOSEVI (sofosbuvir, velpatasvir, and/or voxilaprevir) or VOSEVI, no clinically significant drug interactions have been either observed or are expected when VOSEVI is combined with the following drugs: cobicistat, darunavir, dolutegravir, elvitegravir, emtricitabine, gemfibrozil, ketoconazole, methadone, raltegravir, rilpivirine, ritonavir, tacrolimus, tenofovir alafenamide, or voriconazole (see **DRUG INTERACTIONS**, **Assessment of Drug Interactions**).

Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of sofosbuvir, GS-331007, velpatasvir, and voxilaprevir are shown in Table 6. The effects of sofosbuvir, velpatasvir, voxilaprevir, sofosbuvir/velpatasvir, or VOSEVI on the exposure of coadministered drugs are shown in Table 7.

Table 6. Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir and the Predominant Circulating Metabolite GS-331007, Velpatasvir, and Voxilaprevir in the Presence of the Coadministered Drug[a]

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK with/without Coadministered Drug No Effect=1.00			
Drug	Dosage (mg)	Active Component	Dosage (mg)		Component	C_{max}	AUC	C_{min}
Acid Reducing Agents								
Famotidine	40 single dose simultaneously with VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	35	sofosbuvir	0.96 (0.85, 1.09)	0.94 (0.88, 1.00)	NA
					GS-331007	1.08 (1.03, 1.12)	1.04 (1.02, 1.06)	NA
					velpatasvir	0.91 (0.83, 1.00)	0.90 (0.79, 1.01)	NA
					voxilaprevir	0.90 (0.81, 1.00)	0.98 (0.90, 1.06)	NA
	40 single dose 12 hours prior to VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	36	sofosbuvir	0.93 (0.82, 1.05)	0.87 (0.82, 0.92)	NA
					GS-331007	1.14 (1.10, 1.19)	1.01 (0.99, 1.03)	NA
					velpatasvir	0.87 (0.79, 0.95)	0.85 (0.75, 0.96)	NA
					voxilaprevir	0.90 (0.81, 1.01)	0.94 (0.87, 1.03)	NA

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK with/without Coadministered Drug No Effect=1.00			
Drug	**Dosage (mg)**	**Active Component**	**Dosage (mg)**		**Component**	**C_{max}**	**AUC**	**C_{min}**
Omeprazole	20 once daily 2 hours prior to VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	34	sofosbuvir	0.77 (0.65, 0.91)	0.73 (0.67, 0.79)	NA
					GS-331007	1.27 (1.20, 1.34)	0.97 (0.94, 1.01)	NA
					velpatasvir	0.43 (0.38, 0.49)	0.46 (0.41, 0.52)	NA
					voxilaprevir	0.76 (0.69, 0.85)	0.80 (0.74, 0.87)	NA
	20 once daily 4 hours after VOSEVI	SOF/VEL/ VOX	400/100/100 single dose	34	sofosbuvir	0.94 (0.83, 1.06)	0.82 (0.77, 0.87)	NA
					GS-331007	1.19 (1.13, 1.26)	0.99 (0.97, 1.01)	NA
					velpatasvir	0.49 (0.43, 0.55)	0.49 (0.43, 0.55)	NA
					voxilaprevir	1.08 (0.96, 1.22)	0.95 (0.88, 1.03)	NA
Antifungal Agent								
Ketoconazole	200 twice daily	VEL	100 single dose	12	velpatasvir	1.29 (1.02, 1.64)	1.71 (1.35, 2.18)	NA
Voriconazole	200 twice daily	VOX	100 single dose	24	voxilaprevir	1.13 (0.98, 1.31)	1.84 (1.66, 2.03)	NA
Antihyperlipidemic Agent								
Gemfibrozil	600 twice daily	VOX	100 single dose	24	voxilaprevir	0.98 (0.85, 1.13)	1.11 (1.01, 1.23)	NA
Antimycobacterials								
Rifampin	600 once daily	SOF	400 single dose	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
					GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA
		VEL	100 single dose	12	velpatasvir	0.29 (0.23, 0.37)	0.18 (0.15, 0.22)	NA
		VOX	100 single dose		voxilaprevir	0.91 (0.76, 1.10)	0.27 (0.23, 0.31)	NA
	600 single dose	VEL	100 single dose	12	velpatasvir	1.28 (1.05, 1.56)	1.46 (1.17, 1.83)	NA
		VOX	100 single dose	24	voxilaprevir	11.10 (8.23, 14.98)	7.91 (6.20, 10.09)	NA

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK with/without Coadministered Drug No Effect=1.00			
Drug	Dosage (mg)	Active Component	Dosage (mg)		Component	C_{max}	AUC	C_{min}
HIV Antiretrovirals								
Atazanavir + ritonavir	300 + 100 single dose	SOF/VEL/ VOX	400/100/100 single dose	15	sofosbuvir	1.29 (1.09, 1.52)	1.40 (1.25, 1.57)	NA
					GS-331007	1.05 (0.99, 1.12)	1.25 (1.16, 1.36)	NA
					velpatasvir	1.29 (1.07, 1.56)	1.93 (1.58, 2.36)	NA
					voxilaprevir	4.42 (3.65, 5.35)	4.31 (3.76, 4.93)	NA
Darunavir + ritonavir + emtricitabine/ tenofovir DF	800 + 100 + 200/300 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	sofosbuvir	0.70 (0.62, 0.78)	0.78 (0.73, 0.83)	NA
					GS-331007	1.06 (1.01, 1.10)	1.15 (1.12, 1.19)	NA
					velpatasvir	0.78 (0.73, 0.84)	0.95 (0.88, 1.02)	1.16 (1.07, 1.26)
					voxilaprevir	1.72 (1.51, 1.97)	2.43 (2.15, 2.75)	4.00 (3.44, 4.65)
Dolutegravir	50 once daily	SOF/VEL	400/100 once daily	24	sofosbuvir	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA
					GS-331007	1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
					velpatasvir	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)
Efavirenz/ emtricitabine/ tenofovir DF[b]	600/200/300 once daily	SOF/VEL	400/100 once daily	14	sofosbuvir	1.38 (1.14, 1.67)	0.97 (0.83, 1.14)	NA
					GS-331007	0.86 (0.80, 0.93)	0.90 (0.85, 0.96)	1.01 (0.95, 1.07)
					velpatasvir	0.53 (0.43, 0.64)	0.47 (0.39, 0.57)	0.43 (0.36, 0.52)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide[c]	150/150/200/ 10 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	sofosbuvir	1.27 (1.09, 1.48)	1.22 (1.12, 1.32)	NA
					GS-331007	1.28 (1.25, 1.32)	1.43 (1.39, 1.47)	NA
					velpatasvir	0.96 (0.89, 1.04)	1.16 (1.06, 1.27)	1.46 (1.30, 1.64)
					voxilaprevir	1.92 (1.63, 2.26)	2.71 (2.30, 3.19)	4.50 (3.68, 5.50)
Emtricitabine/ rilpivirine/ tenofovir alafenamide[d]	200/25/25once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	30	sofosbuvir	0.95 (0.86, 1.05)	1.01 (0.97, 1.06)	NA
					GS-331007	1.02 (0.98, 1.06)	1.04 (1.01, 1.06)	NA
					velpatasvir	1.05 (0.96, 1.16)	1.01 (0.94, 1.07)	1.01 (0.95, 1.09)
					voxilaprevir	0.96 (0.84, 1.11)	0.94 (0.84, 1.05)	1.02 (0.92, 1.12)

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, Velpatasvir, and Voxilaprevir PK with/without Coadministered Drug No Effect=1.00			
Drug	Dosage (mg)	Active Component	Dosage (mg)		Component	C_{max}	AUC	C_{min}
Raltegravir + emtricitabine/ tenofovir DF	400 twice daily+200/300 once daily	SOF/VEL	400/100 once daily	30	sofosbuvir	1.09 (0.97, 1.23)	1.16 (1.07, 1.25)	NA
					GS-331007	0.95 (0.91, 0.98)	1.03 (1.00, 1.06)	1.08 (1.04, 1.13)
					velpatasvir	0.97 (0.87, 1.08)	0.98 (0.88, 1.10)	0.97 (0.87, 1.07)
Immunosuppressants								
Cyclosporine	600 single dose	SOF	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
		VEL	100 single dose	12	velpatasvir	1.56 (1.22, 2.01)	2.03 (1.51, 2.71)	NA
		VOX	100 single dose	25	voxilaprevir	19.02 (14.12, 25.62)	9.39 (7.37, 11.96)	NA
Tacrolimus	5 single dose	SOF	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA
Opiate Agonists								
Methadone	30 to 130 daily	SOF	400 once daily	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA

NA = not available/not applicable

a. All interaction studies conducted in healthy volunteers.

b. Administered as ATRIPLA® (efavirenz/emtricitabine/tenofovir DF fixed-dose combination).

c. Administered as GENVOYA® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose single tablet regimen).

d. Administered as ODEFSEY™ (emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose single tablet regimen).

Table 7. Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI[a]

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Coadministered Drug PK with/without Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI No Effect=1.00		
Drug	Dosage (mg)	Active Component	Dosage (mg)		C_{max}	AUC	C_{min}
Antiarrhythmics							
Digoxin	0.25 single dose	VEL	100 once daily	21	1.88 (1.71, 2.08)	1.34 (1.13, 1.60)	NA

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Coadministered Drug PK with/without Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI No Effect=1.00		
Drug	Dosage (mg)	Active Component	Dosage (mg)		C_{max}	AUC	C_{min}
Anticoagulant							
Dabigatran etexilate	75 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 single dose	36	2.87 (2.61, 3.15)	2.61 (2.41, 2.82)	NA
HIV Antiretrovirals							
Darunavir + ritonavir + emtricitabine/ tenofovir DF[b]	darunavir 800 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	0.89 (0.85, 0.94)	0.86 (0.81, 0.91)	0.66 (0.58, 0.74)
	ritonavir 100 once daily				1.60 (1.47, 1.75)	1.45 (1.35, 1.57)	0.80 (0.72, 0.89)
	emtricitabine 200 once daily				0.88 (0.82, 0.94)	0.99 (0.96, 1.03)	1.20 (1.15, 1.26)
	tenofovir DF 300 once daily				1.48 (1.36, 1.61)	1.39 (1.32, 1.46)	1.47 (1.38, 1.56)
Dolutegravir	50 once daily	SOF/VEL	400/100 once daily	24	1.06 (1.01, 1.11)	1.06 (1.01, 1.13)	1.04 (0.98, 1.10)
Efavirenz/ emtricitabine/ tenofovir DF[c]	efavirenz 600 once daily	SOF/VEL	400/100 once daily	15	0.81 (0.74, 0.89)	0.85 (0.80, 0.91)	0.90 (0.85, 0.95)
	emtricitabine 200 once daily				1.07 (0.98, 1.18)	1.07 (1.00, 1.14)	1.10 (0.97, 1.25)
	tenofovir DF 300 once daily				1.77 (1.53, 2.04)	1.81 (1.68, 1.94)	2.21 (2.00, 2.43)
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide[d]	elvitegravir 150 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	29	0.79 (0.75, 0.85)	0.94 (0.88, 1.00)	1.32 (1.17, 1.49)
	cobicistat 150 once daily				1.23 (1.18, 1.28)	1.50 (1.44, 1.58)	3.50 (3.01, 4.07)
	emtricitabine 200 once daily				0.87 (0.84, 0.91)	0.96 (0.94, 0.99)	1.14 (1.09, 1.20)
	tenofovir alafenamide 10 once daily				0.79 (0.68, 0.92)	0.93 (0.85, 1.01)	NA
Emtricitabine/ rilpivirine/tenofovir alafenamide[e]	emtricitabine 200 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	30	0.88 (0.83, 0.93)	0.93 (0.90, 0.96)	1.07 (1.01, 1.14)
	rilpivirine 25 once daily				0.79 (0.74, 0.84)	0.80 (0.76, 0.85)	0.82 (0.77, 0.87)
	tenofovir alafenamide 25 once daily				1.32 (1.17, 1.48)	1.52 (1.43, 1.61)	NA
Raltegravir + emtricitabine/ tenofovir DF	emtricitabine 200 once daily	SOF/VEL	400/100 once daily	30	1.08 (1.04, 1.12)	1.05 (1.03, 1.07)	1.02 (0.97, 1.08)
	tenofovir DF 300 once daily				1.46 (1.39, 1.54)	1.40 (1.34, 1.45)	1.70 (1.61, 1.79)
	raltegravir 400 twice daily				1.03 (0.74, 1.43)	0.97 (0.73, 1.28)	0.79 (0.42, 1.48)

Co-administered Drug		Sofosbuvir (SOF)/ Velpatasvir (VEL)/ Voxilaprevir (VOX)		N	Mean Ratio (90% CI) of Coadministered Drug PK with/without Sofosbuvir, Velpatasvir, Voxilaprevir, or VOSEVI No Effect=1.00		
Drug	Dosage (mg)	Active Component	Dosage (mg)		C_{max}	AUC	C_{min}
HMG-COA Reductase Inhibitors							
Pravastatin	pravastatin 40 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	19	1.89 (1.53, 2.34)	2.16 (1.79, 2.60)	NA
Rosuvastatin	rosuvastatin 10 single dose	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	19	18.88 (16.23, 21.96)	7.39 (6.68, 8.18)	NA
Immunosuppressants							
Cyclosporine	600 single dose	SOF	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
		VEL	100 single dose	12	0.92 (0.82, 1.02)	0.88 (0.78, 1.00)	NA
		VOX	100 single dose	24	0.95 (0.88, 1.03)	0.94 (0.84, 1.06)	NA
Tacrolimus	5 single dose	SOF	400 once daily	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Oral Contraceptives							
Norelgestromin	norgestimate 0.180/0.215/0.250/ ethinyl estradiol 0.025 once daily	SOF/VEL/ VOX + VOX	400/100/100 + 100 once daily	15	1.08 (0.98, 1.19)	1.07 (1.03, 1.12)	1.14 (1.07, 1.21)
Norgestrel					1.15 (1.08, 1.22)	1.15 (1.06, 1.25)	1.22 (1.11, 1.33)
Ethinyl estradiol					1.21 (1.06, 1.38)	1.05 (0.97, 1.15)	0.93 (0.83, 1.04)
Opiate Agonists							
R-Methadone	30 to 130 daily	SOF	400 once daily	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone		SOF	400 once daily	14	0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)

NA = not available/not applicable

a. All interaction studies conducted in healthy volunteers.

b. Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine/tenofovir DF.

c. Administered as ATRIPLA (efavirenz/emtricitabine/tenofovir DF fixed-dose combination).

d. Administered as GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose single tablet regimen).

e. Administered as ODEFSEY (emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose single tablet regimen).

Drug-Food Interactions

VOSEVI should be taken with food. Food increases the bioavailability of VOSEVI (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment** and **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

Drug-Herb Interactions

Coadministration of VOSEVI with St. John's wort is contraindicated.

Coadministration of St. John's wort, a potent P-gp and CYP inducer, may decrease sofosbuvir, velpatasvir, and voxilaprevir plasma concentrations, which may result in loss of therapeutic effect. See **WARNINGS AND PRECAUTIONS**, **General, Use with Potent P-gp Inducers and/or Moderate to Potent Inducers of CYP**.

Drug-Laboratory Interactions

Interactions of VOSEVI with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

VOSEVI is a single tablet regimen. No dosage adjustments are possible for VOSEVI.

The recommended dose of VOSEVI is one tablet of 400 mg/100 mg/100 mg sofosbuvir/velpatasvir/voxilaprevir, taken orally, once daily with food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**, ***Effects of Food***).

The recommended dose and treatment duration for VOSEVI is provided in Table 8.

Table 8. Recommended Treatment Regimen

Genotype	Patients Previously Treated with an HCV Regimen Containing:	VOSEVI Duration
1, 2, 3, 4, 5, or 6	An NS5A inhibitor[a]	12 weeks
1, 2, 3, or 4	Sofosbuvir without an NS5A inhibitor[b]	12 weeks

a. In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.

b. In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

Special Populations

Pediatrics (< 18 Years of age)

VOSEVI is not indicated for use in pediatric patients < 18 years of age.

Geriatrics (≥ 65 years of age)

No dose adjustment is warranted for elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatic Impairment

VOSEVI is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). No dose adjustment of VOSEVI is required for patients with mild hepatic impairment (Child-Pugh A) (see **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Impairment

The safety and efficacy of VOSEVI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or ESRD requiring hemodialysis. No dose adjustment of VOSEVI is required for patients with mild or moderate renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**).

Missed Dose

If a patient misses a dose of VOSEVI within 18 hours of the time it is usually taken, the patient should take VOSEVI as soon as possible, and then take the next dose of VOSEVI at the regularly scheduled time.

If a patient misses a dose of VOSEVI and it is after 18 hours of the time it is usually taken, the patient should not take the missed dose, but resume the usual dosing schedule. A double dose of VOSEVI must not be taken.

If a patient vomits less than 4 hours after taking a dose of VOSEVI, the patient should take another dose of VOSEVI. If a patient vomits more than 4 hours after taking a dose of VOSEVI, the patient should take the next dose at the regularly scheduled time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Administration of activated charcoal may be used to aid in the removal of unabsorbed active substance. General supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient are recommended.

No specific antidote is available for overdose with VOSEVI. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with VOSEVI consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Hemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Hemodialysis is unlikely to result in significant removal of velpatasvir or voxilaprevir since velpatasvir and voxilaprevir are highly bound to plasma protein.

The highest documented doses of sofosbuvir, velpatasvir, and voxilaprevir were single doses of 1200 mg, 500 mg, and 900 mg, respectively. In healthy volunteer studies with sofosbuvir and velpatasvir, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The most common adverse events in subjects receiving voxilaprevir 900 mg were diarrhea (34%), vomiting (19%), and nausea (17%). The effects of higher doses/exposures are not known.

ACTION AND CLINICAL PHARMACOLOGY

Description

VOSEVI is a pan-genotypic single tablet regimen of sofosbuvir, velpatasvir, and voxilaprevir.

Sofosbuvir is a nucleotide analog pan-genotypic NS5B polymerase inhibitor. Velpatasvir is a pan-genotypic HCV NS5A inhibitor. Voxilaprevir is a pan-genotypic inhibitor of the NS3/4A protease.

Mechanism of Action

VOSEVI

Sofosbuvir, velpatasvir and voxilaprevir exhibit high potency and specificity as individual agents against HCV as compounds that target the HCV NS5B, NS5A, and NS3/4A proteins, respectively. Sofosbuvir, velpatasvir, and voxilaprevir individually displayed potent and broad inhibitory activity against HCV genotypes 1-6. *In vitro* combination of sofosbuvir and velpatasvir, sofosbuvir and voxilaprevir, or velpatasvir and voxilaprevir exhibited an additive antiviral interaction. No antiviral antagonism or exacerbated cellular toxicity was observed in either of the 2-drug combinations.

Sofosbuvir

Sofosbuvir is a pan-genotypic polymerase inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Sofosbuvir is a monophosphorylated pyrimidine nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203).

Velpatasvir

Velpatasvir is a pan-genotypic HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. *In vitro* resistance selection and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

Voxilaprevir

Voxilaprevir is a pan-genotypic inhibitor of the HCV NS3/4A protease. Voxilaprevir acts as a noncovalent, reversible inhibitor of the NS3/4A protease.

Pharmacodynamics

Effect on Electrocardiogram

Administration of supratherapeutic doses of sofosbuvir (1200 mg), velpatasvir (500 mg), or voxilaprevir (900 mg) (as individual drugs) demonstrated a lack of effect on QTc interval.

Pharmacokinetics

Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg. Velpatasvir AUC increases in a greater than proportional manner from 5 to 50 mg and in a less than proportional manner from 50 to 450 mg, indicating velpatasvir absorption is solubility limited. Voxilaprevir (studied under fed conditions) AUC increases in a greater than proportional manner over the dose range of 100 to 900 mg.

The pharmacokinetic properties of the components of VOSEVI are provided in Table 9. The multiple dose pharmacokinetic parameters of sofosbuvir and its metabolite, GS-331007, velpatasvir, and voxilaprevir are provided in Table 10.

Table 9 Pharmacokinetic Properties of the Components of VOSEVI

			Sofosbuvir	Velpatasvir	Voxilaprevir
Absorption					
T_{max} (h)			2	4	4
Effect of food (relative to fasting)[a]	Low fat, low calorie[b]	AUC_T	↑ 119%	↑ 181%	↑ 131%
		C_{max}	↑ 73%	↑ 187%	↑ 147%
	Moderate fat, moderate calorie[b]	AUC_T	↑ 146%	↑ 142%	↑ 223%
		C_{max}	↑ 76	↑ 146%	↑ 259%
	High fat, high calorie[c]	AUC_T	↑ 64%	↑ 41%	↑ 542%
		C_{max}	↑ 9	↑ 37%	↑ 679%
Distribution					
% Bound to human plasma proteins			61–65	>99	>99
Blood-to-plasma ratio			0.7	0.5-0.7	0.5-0.8
Metabolism					
Metabolism			Cathepsin A CES1 HINT1	CYP2B6 CYP2C8 CYP3A4	CYP3A4
Elimination					
Major route of elimination			SOF: metabolism GS-331007[d]: glomerular filtration and active tubular secretion	Biliary excretion as parent (77%)	Biliary excretion as parent (40%)
$t_{1/2}$ (h)[e]			SOF: 0.5 GS-331007[d]: 29	17	33
% Of dose excreted in urine[f]			80[e]	0.4	0
% Of dose excreted in feces[f]			14	94	94

CES1 = carboxylesterase 1; HINT1 = histidine triad nucleotide-binding protein 1.

a. Values refer to % increase in geometric mean exposures.
b. Single dose concomitant administration of sofosbuvir/velpatasvir 400 mg/100 mg fixed-dose combination tablet + voxilaprevir 100 mg tablet.
c. Single dose administration of VOSEVI.
d. GS-331007 is the primary circulating nucleoside metabolite of SOF.
e. $t_{1/2}$ values refer to median terminal plasma half-life.
f. Single dose administration of [^{14}C] SOF, [^{14}C] VEL, [^{14}C] VOX in mass balance studies.
g. Predominantly as GS-331007.

Table 10 Multiple Dose Pharmacokinetic Parameters of Sofosbuvir and its Metabolite, GS-331007, Velpatasvir, and Voxilaprevir Following Oral Administration in HCV-Infected Adults

Parameter Mean (%CV)	Sofosbuvir[a]	GS-331007[b]	Velpatasvir[c]	Voxilaprevir[d]
C_{max} (nanogram per mL)	678 (35.4)	744 (28.3)	311 (56.1)	192 (85.8)
AUC_{tau} (nanogram•hr per mL)	1665 (30.1)	12834 (29.0)	4041 (48.6)	2577 (73.7)
C_{trough} (nanogram per mL)	NA	NA	51 (64.7)	47 (82.0)

CV = Coefficient of Variation; NA = Not Applicable.
a. From Population PK analysis, N = 1038.
b. From Population PK analysis, N = 1593.
c. From Population PK analysis, N = 1595.
d. From Population PK analysis, N = 1591.

Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and subjects with HCV infection. Relative to healthy subjects, velpatasvir AUC_{0-24} and C_{max} were 41% lower and 39% lower, respectively, in HCV-infected subjects. Relative to healthy subjects, voxilaprevir AUC_{0-24} and C_{max} were both 260% higher in HCV-infected subjects. Age, sex, race, BMI, or the presence or absence of cirrhosis had no clinically relevant effects on the exposure of sofosbuvir, GS-331007, velpatasvir, or voxilaprevir.

Absorption

Following oral administration of VOSEVI, sofosbuvir median peak plasma concentration was observed 2 hours post-dose. Median peak plasma concentration of GS-331007, velpatasvir, and voxilaprevir were observed 4 hours post-dose.

Effects of Food

The bioavailability of sofosbuvir, velpatasvir and voxilaprevir increased following single dose administration of VOSEVI with a high fat, high calorie meal or concomitant administration of a sofosbuvir/velpatasvir fixed dose combination tablet + voxilaprevir tablet with a low fat, low calorie or a moderate fat, moderate calorie meal (Table 9).

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Velpatasvir is > 99% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09 μg/mL to 1.8 μg/mL. After a single 100 mg dose of [^{14}C]-velpatasvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.5 and 0.7.

Voxilaprevir is approximately > 99% bound to human plasma proteins. After a single 100 mg dose of [^{14}C]-voxilaprevir in healthy male subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.5 and 0.8.

Metabolism

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate, GS-461203. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for greater than 90% of total systemic exposure.

Velpatasvir is primarily a substrate of CYP2B6, CYP2C8, and CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-velpatasvir to healthy human male subjects, the majority (> 98%) of radioactivity in plasma was the parent drug. Unchanged velpatasvir is the major species present in feces.

Voxilaprevir is primarily a substrate of CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-voxilaprevir, the majority (approximately 91%) of radioactivity in plasma was parent drug. Hydrolyzed- and dehydrogenated-voxilaprevir were the major metabolites identified in human plasma. Unchanged voxilaprevir is the major species present in feces.

Excretion

Sofosbuvir is primarily eliminated in the urine as GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of VOSEVI were 0.5 and 29 hours, respectively.

Biliary excretion of parent drug was the major route of elimination for velpatasvir. The median terminal half-life of velpatasvir following administration of VOSEVI was approximately 17 hours.

Biliary excretion of parent drug was the major route of elimination for voxilaprevir. The median terminal half-life of voxilaprevir following administration of VOSEVI was approximately 33 hours.

Special Populations and Conditions

Pediatrics (< 18 years of age)

The pharmacokinetics of VOSEVI in pediatric patients have not been established.

Geriatrics (≥ 65 years of age)

Based on population pharmacokinetic analyses, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007, velpatasvir, or voxilaprevir. Clinical trials of VOSEVI included 74 subjects aged 65 and over (17% of the total number of subjects in the POLARIS-1 and POLARIS-4 Phase 3 clinical trials). The response rates observed for patients ≥ 65 years of age were similar to those of patients < 65 years of age, across treatment groups.

Gender

No clinically relevant pharmacokinetic differences due to gender have been identified for sofosbuvir, GS-331007, velpatasvir, or voxilaprevir.

Race

No clinically relevant pharmacokinetic differences due to race have been identified for sofosbuvir, GS-331007, velpatasvir, or voxilaprevir.

Hepatic Insufficiency

Hepatic impairment studies were conducted with the individual drugs, sofosbuvir, velpatasvir, and voxilaprevir.

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child-Pugh B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, respectively, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Mild hepatic impairment is not expected to meaningfully alter the pharmacokinetics of sofosbuvir and GS-331007. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (Child-Pugh A) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with moderate and severe hepatic impairment (Child-Pugh B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in subjects with moderate hepatic impairment, severe hepatic impairment, and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (Child-Pugh A) had no clinically relevant effect on the exposure of velpatasvir.

The pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative subjects with moderate and severe hepatic impairment (Child-Pugh B and C). Relative to subjects with normal hepatic function, the voxilaprevir AUC_{inf} was 299% and 500% higher in subjects with moderate and severe hepatic impairment, respectively. Population pharmacokinetic analysis in HCV-infected patients indicated that patients with cirrhosis (Child-Pugh A) had 73% higher exposure of voxilaprevir than those without cirrhosis.

Renal Insufficiency

Renal impairment studies have been conducted with the individual drugs, sofosbuvir, velpatasvir, and voxilaprevir.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥ 50 and < 80 mL/min/1.73m^2), moderate (eGFR ≥ 30 and < 50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir AUC_{inf} was 61%, 107%, and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 AUC_{inf} was 55%, 88%, and 451% higher, respectively. In subjects with ESRD, sofosbuvir AUC_{inf} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis. The AUC_{inf} of GS-331007 in subjects with ESRD administered sofosbuvir 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively, compared to normal subjects.

Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. Following a single 400 mg dose of sofosbuvir, a 4-hour hemodialysis session removed approximately 18% of administered dose.

Exposure of velpatasvir is not significantly impacted in the setting of severe renal impairment. The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Velpatasvir AUC and C_{max} were approximately 50% and 11% higher, respectively, in subjects with severe renal impairment compared to control subjects with normal renal function; these differences are not considered clinically relevant.

The pharmacokinetics of voxilaprevir were studied with a single dose of 100 mg voxilaprevir in HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Voxilaprevir AUC and C_{max} were approximately 71% and 45% higher, respectively, in subjects with severe renal impairment compared to control subjects with normal renal function; these differences are not considered clinically significant.

STORAGE AND STABILITY

Store below 30 °C (86 °F).

- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VOSEVI is a single tablet regimen containing sofosbuvir, velpatasvir, and voxilaprevir for oral administration.

Each tablet contains 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir. The tablets include the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: ferrosoferric oxide, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

VOSEVI is available as a beige-colored, capsule-shaped, film-coated tablet debossed with “GSI” on one side and “3” on the other side of the tablet. Each bottle contains 28 tablets, a polyester coil and silica gel desiccant and is closed with a child-resistant closure.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

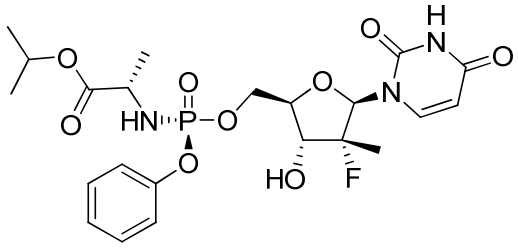
Common name: **sofosbuvir**

Chemical name: (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate

Molecular formula: $C_{22}H_{29}FN_3O_9P$

Molecular mass: 529.45

Structural formula:



Physicochemical properties:

Appearance: Sofosbuvir is a white to off-white crystalline solid.

Solubility: Sofosbuvir is slightly soluble in water.

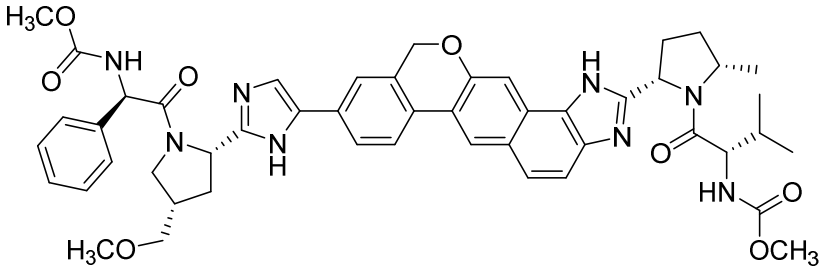
Common name: **velpatasvir**

Chemical name: Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Molecular formula: $C_{49}H_{54}N_8O_8$

Molecular mass: 883.00

Structural formula:



Physicochemical properties:

Appearance: Velpatasvir is a white to tan or yellow solid.

Solubility: Velpatasvir is practically insoluble (< 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2.0, and soluble (> 36 mg/mL) at pH 1.2.

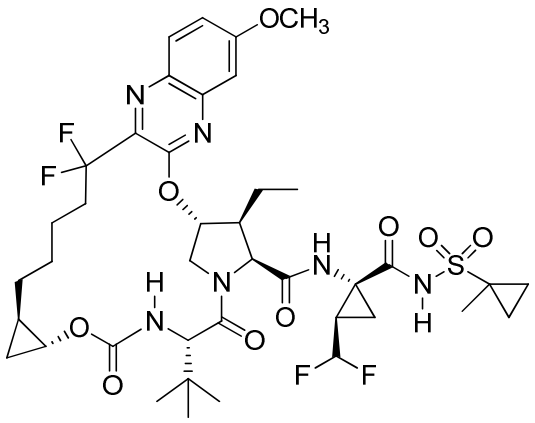
Common name: **voxilaprevir**

Chemical name: (1*aR*,5*S*,8*S*,9*S*,10*R*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropanesulfonyl) carbamoyl]cyclopropyl}-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1*a*,3,4,5,6,9,10,18,19,20,21,22,22*a*-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide

Molecular formula: $C_{40}H_{52}F_4N_6O_9S$ (on solvate-free basis)

Molecular mass: 868.9 (on solvate-free basis)

Structural formula:



Voxilaprevir drug substance is produced from the crystallization, isolation, and drying of the voxilaprevir ethyl acetate solvate.

Physicochemical properties:

Appearance	Voxilaprevir is a white to light brown solid.
Solubility	Voxilaprevir is slightly hygroscopic to hygroscopic. Voxilaprevir is practically insoluble (less than 0.1 mg/mL) below pH 6.8.

CLINICAL TRIALS

The efficacy of VOSEVI was evaluated in two Phase 3 trials with data available for a total of 445 DAA-experienced patients with genotype 1 to 6 HCV infection without cirrhosis or with compensated cirrhosis.

Sustained virologic response (SVR12), defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment, was the primary endpoint to determine the HCV cure rate. Serum HCV RNA values were measured during the clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a LLOQ of 15 IU per mL.

NS5A Inhibitor-Experienced Adults (POLARIS-1)

Trial Design

The trial design of POLARIS-1 is described in Table 11. Patients with genotype 1 HCV infection were randomized in a 1:1 to each group. Randomization was stratified by the presence or absence of cirrhosis. Patients with all other HCV genotypes were enrolled into the VOSEVI 12-week group.

Table 11. Summary of Trial Design in NS5A Inhibitor-Experienced Patients with Genotypes 1, 2, 3, 4, 5, 6 HCV Infection Without Cirrhosis or with Compensated Cirrhosis (POLARIS-1)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, double-blind, placebo-controlled, multicentre	VOSEVI (400 mg/100 mg/100 mg), QD, PO or Placebo, QD, PO	VOSEVI	12 weeks
		Placebo	12 weeks

PO = orally; QD = once a day

Demographics and Other Baseline Characteristics

The demographics and baseline characteristics for the patients in study POLARIS-1 were generally balanced across the treatment groups and are summarized in Table 12. In the POLARIS-1 trial, prior DAA regimens contained the following NS5A inhibitors: ledipasvir (51%), daclatasvir (27%), ombitasvir (11%), velpatasvir (7%), and elbasvir (3%).

Table 12. Demographic and Other Baseline Characteristics of NS5A Inhibitor-Experienced Patients with Genotypes 1, 2, 3, 4, 5, 6 HCV Infection Without Cirrhosis or with Compensated Cirrhosis (POLARIS-1)

Characteristics	VOSEVI 12 Weeks N = 263	Placebo 12 Weeks N = 152
Age (years)		
Mean (range)	58 (27-84)	59 (29-80)
Gender, n (%)		
Male	200 (76)	121 (80)
Female	63 (24)	31 (20)
Race, n (%*)		
White	211 (80)	124 (82)
Black	38 (14)	22 (14)
Asian	8 (3)	6 (4)
Native Hawaiian or Pacific Islander	3 (1)	0
Not disclosed	1 (<1)	0
American Indian or Alaska Native	1 (<1)	0
Other	1 (< 1)	0
BMI, n (%)		
< 30 kg/m^2	179 (68)	100 (66)
≥ 30 kg/m^2	84 (32)	52 (34)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.3 ± 0.7	6.3 ± 0.6
< 800,000 copies/mL, n (%)	73 (28)	36 (24)
≥ 800,000 copies/mL, n (%)	190 (72)	116 (76)
HCV genotype, n (%*)		
1	150 (57)	150 (99)
1a	101 (38)	117 (77)
1b	45 (17)	31 (20)
1 Other	4 (1)	2 (1)
2	5 (2)	0
3	78 (30)	0
4	22 (8)	0
5	1 (<1)	0
6	6 (2)	2 (1)
Unknown	1 (<1)	0
IL28B, n (%*)		
CC	47 (18)	27 (18)
Non-CC	216 (82)	125 (82)
Cirrhosis, n (%*)		
Yes (compensated)	121 (46)	51 (34)
No	142 (54)	101 (66)

Characteristics	VOSEVI 12 Weeks N = 263	Placebo 12 Weeks N = 152
Prior HCV Treatment, n (%)		
DAA-Experienced	263 (100)	152 (100)
NS5A ± DAA(s)	262 (100)	151 (99)
NS5A + NS5B	161 (61)	81 (53)
NS5A + NS3 ± NS5B	83 (32)	61 (40)
NS5A ± Others	18 (7)	9 (6)
Others	1 (<1)	1 (1)

DAA = direct-acting antiviral; SD = standard deviation
*Total percentage may not add to 100% due to rounding.

Study Results

The response rates for the VOSEVI treatment group by HCV genotype in the POLARIS-1 trial are presented in Table 13. Overall, the SVR12 in NS5A inhibitor-experienced patients with genotypes 1, 2, 3, 4, 5, 6 HCV infection with compensated cirrhosis or without cirrhosis was 96%. Treatment with VOSEVI for 12 weeks in POLARIS-1 was statistically superior relative to the pre-specified performance goal of 85% ($p < 0.001$). No patient in the placebo group achieved SVR.

Table 13. SVR12 and Virologic Outcome in NS5A Inhibitor-Experienced Patients with Genotypes 1, 2, 3, 4, 5, 6 HCV Infection Without Cirrhosis or with Compensated Cirrhosis (POLARIS-1)

	VOSEVI 12 Weeks (N=263)								
	Total (all GTs)[a] (N=263)	GT-1			GT-2 (N=5)	GT-3 (N=78)	GT-4 (N=22)	GT-5 (N=1)	GT-6 (N=6)
		GT-1a (N=101)	GT-1b (N=45)	Total[b] (N=150)					
SVR12	96% (253/263)	96% (97/101)	100% (45/45)	97% (146/150)	100% (5/5)	95% (74/78)	91% (20/22)	100% (1/1)	100% (6/6)
Outcome for Patients without SVR									
On-Treatment Virologic Failure[c]	<1% (1/263)	1% (1/101)	0/45	1% (1/150)	0/5	0/78	0/22	0/1	0/6
Relapse[d]	2% (6/261)	1% (1/100)	0/45	1% (1/149)	0/5	5% (4/78)	5% (1/21)	0/1	0/6
Other[e]	1% (3/263)	2% (2/101)	0/45	1% (2/150)	0/5	0/78	5% (1/22)	0/1	0/6

GT = genotype; SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 15 IU/mL) at 12 weeks after the cessation of treatment.

a. One patient with undetermined genotype achieved SVR12.
b. Four patients had GT-1 subtypes other than GT-1a or GT-1b; all 4 patients achieved SVR12.
c. Pharmacokinetic data for the 1 patient with on-treatment virologic failure was consistent with non-adherence.
d. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
e. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. High SVR12 rates were achieved in all subgroups, regardless of the presence of cirrhosis (Table 14) or prior DAA class combinations or specific DAA combinations.

Table 14. SVR12 for NS5A Inhibitor-Experienced Patients with Genotypes 1, 2, 3, 4, 5, 6 HCV Infection Without Cirrhosis or With Compensated Cirrhosis (POLARIS-1)

	VOSEVI 12 Weeks N = 263									
	All GTs[a] (N=263) % (n/N)	GT-1				GT-2 (N=5) % (n/N)	GT-3 (N=78) % (n/N)	GT-4 (N=22) % (n/N)	GT-5 (N=1) % (n/N)	GT-6 (N=6) % (n/N)
		GT-1a (N=101) % (n/N)	GT-1b (N=45) % (n/N)	GT-1 Other (N=4) % (n/N)	GT-1 Total (N=150) % (n/N)					
Cirrhosis	93 (113/121)	94 (31/33)	100 (16/16)	100 (2/2)	96 (49/51)	0/0	93 (52/56)	86 (12/14)	0/0	0/0
No Cirrhosis	99 (140/142)	97 (66/68)	100 (29/29)	100 (2/2)	98 (97/99)	100 (5/5)	100 (22/22)	100 (8/8)	100 (1/1)	100 (6/6)

GT = genotype
a. One patient with undetermined genotype without cirrhosis achieved SVR12.

DAA-Experienced Adults Who Had Not Received an NS5A Inhibitor (POLARIS-4)

Trial Design

The trial design of POLARIS-4 is described in Table 15. Patients with genotype 1, 2, or 3 HCV infection were randomized 1:1 to each group. Randomization was stratified by HCV genotype and by the presence or absence of cirrhosis. Patients with genotype 4 HCV infection were enrolled to the VOSEVI 12-week group. Patients whose only DAA exposure was a NS3/4A protease inhibitor were excluded.

Table 15. Summary of Trial Design in DAA-Experienced Patients with Genotype 1, 2, 3, or 4 HCV Infection Without Cirrhosis or With Compensated Cirrhosis who had Not Received an NS5A Inhibitor (POLARIS-4)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	VOSEVI (400 mg/100 mg/100 mg), QD, PO or SOF/VEL (400 mg/100 mg), QD, PO	VOSEVI	12 weeks
		SOF/VEL	12 weeks

PO = orally; QD = once a day; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir

Demographic and Baseline Characteristics

The demographics and baseline characteristics for the patients in study POLARIS-4 were balanced across the treatment groups and are summarized in Table 16. In the POLARIS-4 trial, prior DAA regimens contained sofosbuvir (85%) with the following: peginterferon alfa and ribavirin or ribavirin (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (<1%). Of the 15% of subjects without prior sofosbuvir exposure, most received investigational HCV DAAs or approved HCV NS3/4A protease inhibitors, with or without peginterferon alfa and ribavirin.

Table 16. Demographic and Other Baseline Characteristics of DAA-Experienced Patients with Genotype 1, 2, 3, or 4 HCV Infection Without Cirrhosis or With Compensated Cirrhosis who had Not Received an NS5A Inhibitor (POLARIS-4)

Characteristics	VOSEVI 12 Weeks N = 182	SOF/VEL 12 Weeks N = 151
Age (years)		
Mean (range)	57 (24-85)	57 (24-80)
Gender, n (%*)		
Male	143 (79)	114 (75)
Female	39 (21)	37 (24)
Race, n (%*)		
White	160 (88)	131 (87)
Black	16 (9)	13 (9)
Asian	2 (1)	4 (3)
Other	2 (1)	1 (1)
American Indian or Alaska Native	2 (1)	0
Native Hawaiian or Pacific Islander	0	2 (1)
BMI, n (%)		
< 30 kg/m^2	120 (66)	98 (65)
≥ 30 kg/m^2	62 (34)	53 (35)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.3 ± 0.6	6.3 ± 0.7
< 800,000 copies/mL, n (%)	46 (25)	38 (25)
≥ 800,000 copies/mL, n (%)	136 (75)	113 (75)
HCV genotype, n (%)		
1	78 (43)	66 (44)
1a	54 (30)	44 (29)
1b	24 (13)	22 (15)
2 (no confirmed subtype)	31 (17)	33 (22)
3	54 (30)	52 (34)
4	19 (10)	0/0
IL28B, n (%)		
CC	33 (18)	29 (19)
Non-CC	149 (82)	122 (81)
Cirrhosis, n (%)		
Yes (compensated)	84 (46)	69 (46)
No	98 (54)	82 (54)

Characteristics	VOSEVI 12 Weeks N = 182	SOF/VEL 12 Weeks N = 151
Prior HCV Treatment Experience, n (%*)		
DAA-Naïve	0	1 (<1)
DAA-Experienced	182 (100)	150 (99)
NS5B only	134 (74)	109 (72)
NS5B + NS3	46 (25)	38 (25)
Others	2 (1)	3 (2)

SD = standard deviation
*Total percentage may not add to 100% due to rounding.

Study Results

Overall, the SVR12 rate in DAA-experienced patients with genotype 1, 2, 3, 4 HCV infection without cirrhosis or with compensated cirrhosis who had not received an NS5A inhibitor was 98%. Table 17 presents the SVR12 by HCV genotype and virologic outcome for the POLARIS-4 trial. Treatment with VOSEVI for 12 weeks in POLARIS-4 was statistically superior to the SVR12 performance goal of 85% at the pre-specified 0.025 significance level ($p < 0.001$). Treatment with SOF/VEL for 12 weeks was not statistically superior to a performance goal of 85% at the pre-specified 0.025 significance level ($p = 0.092$).

Table 17. SVR12 and Virologic Outcome in DAA-Experienced Patients with Genotype 1, 2, 3, or 4 HCV Infection Without Cirrhosis or With Compensated Cirrhosis who had Not Received an NS5A Inhibitor (POLARIS-4)

	VOSEVI 12 Weeks (N=182)	SOF/VEL 12 Weeks (N=151)
Overall SVR12	98% (178/182)	90% (136/151)
Genotype 1	97% (76/78)	91% (60/66)
Genotype 1a	98% (53/54)	89% (39/44)
Genotype 1b	96% (23/24)	95% (21/22)
Genotype 2	100% (31/31)	97% (32/33)
Genotype 3	94% (52/54)	85% (44/52)
Genotype 4	100% (19/19)	0/0
Outcome for Patients without SVR		
On-Treatment Virologic Failure	0/182	1% (1/151)
Relapse[a]	1% (1/182)	9% (14/150)
Other[b]	2% (3/182)	0/151

SOF = sofosbuvir; VEL = velpatasvir; SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 15 IU/mL) at 12 weeks after the cessation of treatment.
a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes patients with missing data and those who discontinued treatment prior to virologic suppression.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. High SVR12 rates were achieved in all subgroups in the VOSEVI 12-week group, regardless of the presence of cirrhosis (Table 18) or prior DAA class combinations or specific DAA combinations.

Table 18. SVR12 for DAA-Experienced Patients with Genotype 1, 2, 3, or 4 HCV Infection Without Cirrhosis or With Compensated Cirrhosis who had Not Received an NS5A Inhibitor (POLARIS-4)

	VOSEVI 12 Weeks N = 182						
	All GTs (N=182) % (n/N)	GT-1			GT-2 (N=31) % (n/N)	GT-3 (N=54) % (n/N)	GT-4 (N=19) % (n/N)
		GT-1a (N=54) % (n/N)	GT-1b (N=24) % (n/N)	GT-1 Total (N=78) % (n/N)			
Cirrhosis	96 (81/84)	94 (16/17)	100 (11/11)	96 (27/28)	100 (13/13)	97 (30/31)	100 (12/12)
No Cirrhosis	98 (96/98)	100 (37/37)	92 (12/13)	98 (49/50)	100 (18/18)	96 (22/23)	100 (7/7)

NA = not applicable

Overall in the POLARIS-1 and POLARIS-4 studies, the presence of baseline NS3, NS5A, and NS5B NI RAVs did not alter the SVR12 rates for DAA-experienced patients who received 12 weeks of VOSEVI (see **MICROBIOLOGY**).

MICROBIOLOGY

Antiviral Activity in Cell Culture

The EC_{50} values of sofosbuvir, velpatasvir, and voxilaprevir against full-length or chimeric replicons encoding NS5B, NS5A, and NS3 protease sequences from the laboratory strains are presented in Table 19. The EC_{50} values of sofosbuvir, velpatasvir, and voxilaprevir against clinical isolates are presented in Table 20.

Table 19 Activity of Sofosbuvir, Velpatasvir, and Voxilaprevir Against Full Length or Chimeric Laboratory Replicons

Replicon Genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]	Voxilaprevir EC_{50}, nM[a]
1a	40	0.014	3.9[e]
1b	110	0.016	3.3[e]
2a	50	0.005-0.016[c]	3.7-4.5[e]
2b	15[b]	0.002-0.006[c]	1.8-6.6[f]
3a	50	0.004	6.1[f]
4a	40	0.009	2.9[e]

Replicon Genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]	Voxilaprevir EC_{50}, nM[a]
4d	33	0.004	3.2[e]
5a	15[b]	0.021-0.054[d]	1.9[f]
6a	14-25[b]	0.006-0.009	3.0-4.0[e]
6e	NA	0.130[d]	0.33[f]
6n	NA	NA	2.9[f]

NA = not available

a. Mean value from multiple experiments of same laboratory replicon.

b. Stable chimeric 1b replicons carrying NS5B genes from genotype 2b, 5a or 6a were used for testing.

c. Data from various strains of full length NS5A replicons or chimeric NS5A replicons carrying full-length NS5A genes that contain L31 or M31 polymorphisms.

d. Data from a chimeric NS5A replicon carrying NS5A amino acids 9-184.

e. Stable cell lines expressing Renilla luciferase-encoding replicons.

f. Data obtained from transiently transfected replicons.

Table 20 Activity of Sofosbuvir, Velpatasvir, and Voxilaprevir Against Transient Replicons Containing NS5A, NS5B, or NS3 Protease from Clinical Isolates

	Replicons containing NS5B from clinical isolates		Replicons containing NS5A from clinical isolates		Replicons containing NS3 protease from clinical isolates	
Replicon Genotype	Number of clinical isolates	Median sofosbuvir EC_{50}, nM (range)	Number of clinical isolates	Median velpatasvir EC_{50}, nM (range)	Number of clinical isolates	Median voxilaprevir EC_{50}, nM (range)
1a	67	62 (29-128)	23	0.019 (0.011-0.078)	58	0.59 (0.14-19.16)
1b	29	102 (45-170)	34	0.012 (0.005-0.500)	29	0.50 (0.19-2.87)
2a	1	28	8	0.011 (0.006-0.364)	18	2.8 (1.78-6.72)
2b	14	30 (14-81)	16	0.002 (0.0003-0.007)	43	2.1 (0.92-8.3)
3a	106	81 (24-181)	38	0.005 (0.002-1.871)	32	6.3 (1.3-21.48)
4a	NA	NA	5	0.002 (0.001-0.004)	58	0.52 (0.12-1.7)
4d	NA	NA	10	0.007 (0.004-0.011)	11	0.85 (0.41-1.1)
4r	NA	NA	7	0.003 (0.002-0.006)	1	1.15 NA
5a	NA	NA	42	0.005 (0.001-0.019)	16	1.8 (0.87-5.63)

6a	NA	NA	26	0.007 (0.0005-0.113)	15	2.7 (0.23-7.35)
6e	NA	NA	15	0.024 (0.005-0.433)	12	0.2 (0.12-0.43)

NA = not available

The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir, but reduced the anti-HCV activity of velpatasvir and voxilaprevir by 13- and 6.8-fold, respectively, against genotype 1a HCV replicons.

Evaluation of sofosbuvir in combination with velpatasvir or voxilaprevir, as well as the combination of velpatasvir and voxilaprevir, showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a, and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of genotype 1 to 6 conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, the ability of the active triphosphate of sofosbuvir (GS-461203) to inhibit recombinant NS5B polymerase from genotypes 1b, 2a, 3a, and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In vitro selection of HCV replicons with reduced susceptibility to velpatasvir was performed in cell culture for multiple genotypes including 1a, 1b, 2a, 3a, 4a, 5a, and 6a. Variants were selected at NS5A resistance associated positions 24, 28, 30, 31, 32, 58, 92, and 93. The resistance associated variants (RAVs) selected in 2 or more genotypes were F28S, L31I/V, and Y93H. From site-directed mutagenesis studies, NS5A RAVs that showed a > 2.5-fold reduction in velpatasvir susceptibility are listed in Table 21 below. No individual substitutions tested in genotypes 2a, 4a, or 5a conferred a >100-fold reduction in velpatasvir susceptibility. Combinations of variants often showed greater reductions in susceptibility to velpatasvir than single RAVs alone.

Table 21. Phenotypic Change of Genotype 1-6 NS5A Substitutions to Velpatasvir

Genotype	> 2.5-100-fold*	> 100-fold*
1a	M28A/T, Q30E/G/K, L31F/I/M/V, P32L, H58D, Y93C/L/S/T	M28G, A92K, Y93H/N/R/W
1b	Q24K, L31F/I, P58T, Y93H/N/T	A92K
2a	F28S, L31V, C92R, Y93H/N	None

Genotype	> 2.5-100-fold*	> 100-fold*
2b	L28F, P58A, C92S, Y93F	C92T, Y93H/N
3a	A30H/K, L31F/M, P58G	Y93H
4a	L28T, Y93H/N/S	None
5a	L31I	None
6a	F28M/V, L31I/M, T58G/H, A92T, T93A/H/N/S	L31V, P32A/L/Q/R

*Fold change was calculated as the ratio of mutant EC_{50} to wild-type EC_{50}.

HCV genotype 1a, 1b, 2a, 3a, 4a, 5a, and 6a replicon variants with reduced susceptibility to voxilaprevir were selected in cell culture. Variants were selected at NS3 resistance associated positions 41, 156, and 168. The RAVs selected in 2 or more genotypes were Q41H, A156V/T/L, and D168E/H/Y. From site-directed mutagenesis studies, NS3 RAVs that showed a > 2.5-fold reduction in voxilaprevir susceptibility are listed in Table 22 below. No individual substitutions tested in genotypes 5a, or 6a conferred a > 100-fold reduction in voxilaprevir susceptibility. Combinations of variants often showed greater reductions in susceptibility to voxilaprevir than single RAVs alone.

Table 22. Phenotypic Change of Genotype 1-6 NS3 Substitutions to Voxilaprevir

Genotype	> 2.5-100-fold*	> 100-fold*
1a	V36G, Q41R, F43S, R155G/W, D168A/F/I/K/L/R/T/V	A156L/T
1b	V36A/M, S122D, R155W, A156S, D168V/Y, V170A,	A156T/V
2a	F43V, A156T	A156L/V
3a	Q41K, Q80K, L175M	A156T/V
4a	Q41R, D168E/T/V	A156L/T/V
5a	D168A/H/K/R/Y	None
6a	Q41K/R, Y56H, D168A/H	None

*Fold change was calculated as the ratio of mutant EC_{50} to wild-type EC_{50}.

In Clinical Trials

Of the 263 NS5A inhibitor-experienced patients treated with VOSEVI for 12 weeks in POLARIS-1, 7 of 263 (3%) patients (2 with genotype 1, 4 with genotype 3, and 1 with genotype 4) did not achieve SVR12 and qualified for resistance analysis; 6 relapsed and 1 experienced virologic breakthrough with pharmacokinetic data consistent with nonadherence. The patient with genotype 1a and virologic breakthrough developed the NS5A RAVs L31M and Y93H. One patient with genotype 4d who relapsed developed the NS5A RAV Y93H. No NS3, NS5A, or NS5B nucleoside analog (NI) RAVs emerged in the other 5 patients who relapsed.

Of the 182 DAA-experienced patients treated with VOSEVI for 12 weeks in POLARIS-4, 1 of 182 (1%) patients relapsed and qualified for resistance analysis. No NS3, NS5A, or NS5B NI RAVs emerged in this patient infected with genotype 1a HCV.

Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome

Analyses were conducted to explore the association between pre-existing baseline NS3 and NS5A RAVs and treatment outcome for patients that had previously been treated with DAA regimens in POLARIS-1 and POLARIS-4. Patients were included in the analysis if they had a known virologic outcome. Of the patients treated with VOSEVI for 12 weeks, 260 of 263 in POLARIS-1 and 179 of 182 in POLARIS-4 were included in the analysis of NS3 and NS5A RAVs. Overall, 205 of 260 (79%) patients from POLARIS-1 and 83 of 179 (46%) patients from POLARIS-4 had HCV with NS3 and/or NS5A RAVs at baseline.

SVR12 rates in patients with or without baseline NS3 and/or NS5A RAVs in the POLARIS-1 and POLARIS-4 trials are shown in Table 23.

Table 23 SVR12 in DAA-Experienced Patients with or without Baseline NS3 or NS5A RAVs by Study

	VOSEVI 12 Weeks	
	POLARIS-1 (N=260)	**POLARIS-4 (N=179)**
No NS3 or NS5A RAVs	98% (42/43)	99% (85/86)
Any NS3 or NS5A RAV	97% (199/205)	100% (83/83)
NS3 Only	100% (9/9)	100% (39/39)
NS5A Only	97% (120/124)	100% (40/40)
NS3 and NS5A	97% (70/72)	100% (4/4)
RAVs Not Determined for Both NS3 and NS5A[a]	100% (12/12)	100% (10/10)

a. Patients with NS3 and/or NS5A gene sequencing failure.

SVR12 was achieved in 18 of 19 (95%) patients who had baseline NS5B NI RAVs in POLARIS-1, including 2 patients that had virus with the S282T NS5B NI RAV in addition to NS5A RAVs at baseline. In POLARIS-4, a total of 14 patients had virus with NS5B NI RAVs at baseline and all achieved SVR12.

Cross Resistance

Voxilaprevir is active *in vitro* against most of the NS3 RAVs that confer resistance to first generation NS3/4A protease inhibitors. Additionally, velpatasvir is active *in vitro* against most of the NS5A RAVs that confer resistance to ledipasvir and daclatasvir. Sofosbuvir, velpatasvir, and voxilaprevir were fully active against substitutions associated with resistance to other classes of DAAs with different mechanisms of actions; e.g., voxilaprevir was fully active against NS5A and NS5B NI RAVs.

TOXICOLOGY

Repeat-Dose Toxicity

Sofosbuvir

Sofosbuvir or GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer, was evaluated in repeat-dose oral toxicity studies up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The primary sofosbuvir target organs identified were the gastrointestinal (GI) and hematopoietic (erythroid) systems. In a 7-day toxicity dog study with GS-9851, a dose of 1500 mg/kg/day resulted in (but were not limited to) increased mucus secretions in the stomach, glycogen depletion, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, with associated histopathologic liver findings and increased QT/QTc intervals in dogs. At the adverse dose, GS-331007 exposure levels in the dog study were at least 69-fold higher than HCV-infected patients treated once daily with VOSEVI. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), sofosbuvir effects included (but were not limited to) GI-related clinical signs (e.g., soft feces and emesis) and a decrease (e.g., approximately 10%) in mean red cell indices that were observed mainly in the high-dose group of dogs. One male dog was euthanized moribund with intestinal hemorrhage. The relationship to sofosbuvir was undetermined. In general, exposure levels in the chronic toxicity studies at the no observed adverse effect level were at least 5-fold (based on AUC of GS-331007) higher than HCV-infected patients treated once daily with VOSEVI.

Velpatasvir

Velpatasvir was well tolerated in studies for up to 4 weeks in the mouse, 26 weeks in the rat, and 39 weeks in the dog. No target organs were identified at the highest dose evaluated in each respective repeat dose toxicity study, corresponding to exposure margins of 54-, 3-, and 7-fold greater in mice, rats, and dogs, respectively, than those in HCV-infected patients treated once daily with VOSEVI.

Voxilaprevir

Voxilaprevir was evaluated in repeat-dose oral toxicity studies up to 26 weeks in rats and up to 39 weeks in dogs. The potential target organ/tissues identified for voxilaprevir were the GI tract (rat, dog), hepatobiliary system (rat, dog), hematological system (rat), and renal system (rat, dog). Minimal hematological changes indicative of mild blood loss and an appropriate regenerative response were also observed in the rat. Observed changes were minimal in nature

and considered nonadverse. Voxilaprevir exposures at the no observed adverse effect levels from the chronic repeat-dose toxicity studies in rats and dogs were approximately 244-, and 96-fold higher, respectively, than HCV-infected patients treated once daily with VOSEVI.

Genotoxicity and Carcinogenicity

Sofosbuvir

Sofosbuvir, when administered as the diastereomeric mixture GS-9851, was not genotoxic in a bacterial mutagenicity assay, in an *in vitro* chromosome aberration test using human peripheral blood lymphocytes and in an *in vivo* mouse micronucleus assay.

Sofosbuvir was not carcinogenic in the 2-year mouse and rat carcinogenicity studies at doses resulting in GS-331007 exposures up to 17-fold in mice and 10-fold in rats, higher than human exposure at 400 mg dose.

Velpatasvir

Velpatasvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and *in vivo* rat micronucleus assays.

Velpatasvir was not carcinogenic in a 26-week mouse study at exposures up to 42- and 67-fold higher than human exposure in male and female mice, respectively. A carcinogenicity study in rats is ongoing.

Voxilaprevir

Voxilaprevir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and *in vivo* rat micronucleus assays.

Carcinogenicity studies for voxilaprevir have not been conducted.

Fertility

Sofosbuvir

Sofosbuvir had no effects on fertility when evaluated in rats at exposures (AUC) to the predominant circulating metabolite GS-331007 of at least 4-fold the exposure in humans at the recommended clinical dose.

Velpatasvir

Velpatasvir had no adverse effects on fertility in rats at AUC exposure 4-fold higher than the human exposure at the recommended clinical dose.

Voxilaprevir

Voxilaprevir had no adverse effects on fertility in rats at AUC exposures 149-fold higher than the human exposure at the recommended clinical dose.

REFERENCES

1. Sovaldi (tablet, 400 mg sofosbuvir), submission control number 202358, Product Monograph, Gilead Sciences Canada, Inc. April 28, 2017

2. Epclusa (tablet, 400 mg sofosbuvir/100 mg velpatasvir), submission control number 202377, Product Monograph, Gilead Sciences Canada, Inc. May 8, 2017

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

VOSEVI™
sofosbuvir/velpatasvir/voxilaprevir tablets

Read this carefully before you start taking **Vosevi**. Read it again every time you get a refill. This leaflet is a summary. It will not tell you everything about this drug. Talk to your doctor about your medical condition and treatment. Ask whether there is any new information about **Vosevi**.

Serious Warnings and Precautions

Hepatitis B activity (eg, inflamed liver) may increase when taking antiviral drugs like **Vosevi**, sometimes leading to liver failure and death. (See the "To help avoid side effects…" section, *Hepatitis B Reactivation*)

What is Vosevi used for?
Vosevi is used to treat chronic (long-lasting) hepatitis C in adults who have:
- genotype 1, 2, 3, 4, 5, or 6 infection and have been previously treated with a type of medicine called an NS5A inhibitor.
- genotype 1, 2, 3 or 4 infection and have been previously treated with sofosbuvir without another medicine called an NS5A inhibitor.

How does Vosevi work?
Vosevi contains three medicines put together into one tablet (pill).

- **Vosevi** blocks the hepatitis C virus from making more copies of itself in the body.
- **Vosevi** cures chronic hepatitis C in most patients. Cure means the virus is no longer in your blood 3 months after finishing the medicine.
- Curing chronic hepatitis C virus can help lower the chance you will have liver problems or die from liver disease.

What are the ingredients in Vosevi?
Each tablet has the following medicines: sofosbuvir, velpatasvir, voxilaprevir
Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.
Each tablet is covered with the following ingredients that are not medicines: ferrosoferric oxide, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Vosevi comes in the following dosage forms:
Vosevi comes in beige tablets. Each tablet contains sofosbuvir (400 mg), velpatasvir (100 mg),

and voxilaprevir (100 mg).

Do not use Vosevi if:
- You are allergic to sofosbuvir (also called **Sovaldi**® when it is used alone), velpatasvir (also called **Epclusa™** when it is used with sofosbuvir), voxilaprevir, or any of the other ingredients in this product. (Read also "**What are the ingredients in Vosevi?**" above.)
- You are taking any of the following medicines or natural substances:
    - dabigatran etexilate (Pradaxa®), a drug used to treat blood clots.
    - rifampin (Rifadin®, Rifater®, Rofact®), a drug used to treat tuberculosis.
    - phenobarbital, a drug used to treat anxiety and to control seizures.
    - phenytoin (Dilantin®), a drug used to control seizures.
    - rosuvastatin (Crestor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
    - St. John's wort (*Hypericum perforatum*), an herbal product used for anxiety or depression.

To help avoid side effects and ensure you take your medicine properly, talk to your doctor before you take Vosevi. Talk about any health problems you may have, including if you:
- have liver problems other than hepatitis C infection.
- have HIV.
- have severe kidney disease or you are on dialysis.
- are taking heart medication such as amiodarone (eg, Cordarone®). Your doctor may monitor your heart function while taking **Vosevi** (see "**The following may interact with Vosevi**").
- were born with the rare problem of not being able to tolerate galactose (severe lack of lactase or cannot absorb glucose or galactose). **Vosevi** has lactose.

Other warnings you should know about:

Hepatitis B Reactivation:

Taking antiviral drugs such as **Vosevi** may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Contact your doctor if:

- you have never been tested for hepatitis B.
- you know you have a current hepatitis B infection.
- you have had a previous hepatitis B infection.

Your healthcare professional may do blood tests:

- before hepatitis C treatment.
- to see the hepatitis B levels in your blood.
- and may order hepatitis B treatment.

Pregnancy:
- If you are pregnant or plan to become pregnant, talk to your doctor before you take this medicine. The effects of **Vosevi** during pregnancy are not known. Avoid pregnancy while

taking **Vosevi**. Tell your doctor if you become pregnant while taking **Vosevi**.

Breastfeeding:
- If you are breastfeeding or plan to breastfeed, talk to your doctor about the best way to feed your baby. Do not breastfeed while taking **Vosevi**.

Products containing sofosbuvir:
Because **Vosevi** already contains sofosbuvir, do not take **Vosevi** with any other medicines that have sofosbuvir (e.g., **Sovaldi**, **Harvoni**®, **Epclusa**).

Tell your doctor or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Vosevi:
- amiodarone (Cordarone®), a drug used to treat irregular heartbeats.
- atazanavir (Reyataz®), a drug used to treat HIV.
- atorvastatin (Lipitor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- carbamazepine (Tegretol®), a drug used to treat seizures, nerve pain, and bipolar disorder.
- cyclosporine (Neoral®, Sandimmune® I.V.), a drug used to suppress the immune system.
- digoxin (Lanoxin®, Toloxin®), a drug used to treat congestive heart failure and a certain abnormal heart rhythm (atrial fibrillation).
- efavirenz (Sustiva®, **Atripla**®), a drug used to treat HIV.
- fluvastatin (Lescol®, Lescol® XL), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- lopinavir, a drug used to treat HIV.
- lovastatin (Advicor®*, Mevacor®*), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- medicines for indigestion, heartburn, or ulcers. Examples are nizatidine (Axid®), famotidine (Pepcid AC®, Peptic Guard®, Ulcidine®), cimetidine (Tagamet®), ranitidine (Zantac®), esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Losec®), rabeprazole (Aciphex®) and pantoprazole (Pantoloc®) or antacids (like Tums®, Rolaids® or Alka-Seltzer®) that have an ingredient to protect the stomach.
- ethinyl estradiol, a drug in some oral contraceptives used to prevent pregnancy (eg, Alesse®, Apri®, Aviane®, Marvelon®, Seasonale®, Tri-Cyclen®, Yasmin®, Yaz®).
- oxcarbazepine (Trileptal®), a drug used to control seizures.
- pravastatin (Pravachol®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- rifabutin (Mycobutin®), a drug used to treat tuberculosis.
- rifapentine*, a drug used to treat tuberculosis.
- simvastatin (Zocor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- tenofovir disoproxil fumarate (**Atripla**, **Complera**®, **Stribild**®, **Truvada**®, **Viread**®), to treat HIV.
- warfarin (Coumadin®) or other similar medicines called vitamin K antagonists, to thin the

blood. Your doctor may need to test your blood more often to check how well your blood can clot.

*Not sold in Canada.

How to take Vosevi:

- Take this medicine with food.
- If you are taking an antacid, you may need to take **Vosevi** at a different time than the antacid. Talk to your doctor or pharmacist.
- Do NOT stop taking **Vosevi** without first talking with your doctor.

Usual adult dose:

- Take one tablet once daily for 12 weeks.

Overdose:

If you think you have taken too much **Vosevi**, contact your doctor or pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

It is important to take **Vosevi** each day.

- **If you miss a dose** of **Vosevi** and you notice within 18 hours, take a tablet as soon as you can. Then take the next dose at your usual time.
- **If you miss a dose** of **Vosevi** and you notice after 18 hours, wait and take the next dose at your usual time. Do NOT take a double dose (two doses close together).

What to do if you vomit (throw up):

- If you vomit **less than 4 hours** after taking **Vosevi**, take another tablet.
- If you vomit **more than 4 hours** after taking **Vosevi**, wait. Do NOT take another tablet until you are scheduled to take the next tablet.

What are possible side effects from using Vosevi?

These are not all the possible side effects you may feel when taking **Vosevi**. If your side effect is not listed here, contact your doctor or pharmacist.

The most common side effects of **Vosevi** are headache, feeling tired, diarrhea, feeling sick in the stomach, problem with getting to sleep, and less energy or strength.

When sofosbuvir (one of the medicines in **Vosevi**) is used with other hepatitis C medicines (eg, daclatasvir [Daklinza™], simeprevir [Galexos®], or ledipasvir) and amiodarone (a heart drug), side effects may be:

- slow heartbeat leading to a need for a pacemaker or death.

Contact your doctor immediately if you have symptoms of a slow heartbeat such as:

- fainting or near-fainting.
- dizziness or lightheadedness.
- not feeling well.
- feeling weak or very tired.
- shortness of breath.
- chest pains.
- confusion or memory problems.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your doctor.

Reporting side effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store **Vosevi** below 30 ^{o}C (86 ^{o}F).
- Keep **Vosevi** in its original container.
- Do NOT use **Vosevi** if the seal over the bottle opening is broken or missing.
- Keep this medication where children cannot reach it or see it.

If you want more information about Vosevi:

- Talk to your doctor or pharmacist.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-

products/drug-product-database.html); the manufacturer's website (www.gilead.ca), or by calling 1-800-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

Last Revised: August 16, 2017

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USA

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Mississauga, ON L5N 2W3

e192340-GS-000

THE ATTACHED IS EXHIBIT "J" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 13TH DAY OF OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMAVIRET™

glecaprevir/pibrentasvir
tablets (100/40 mg)

Antiviral Agent

Date of Preparation:
January 25, 2017

AbbVie Corporation
8401 Trans-Canada Highway
St-Laurent, QC H4S 1Z1

Date of Revision:
August 16, 2017

Submission Control No: 202233

Table of Contents

MAVIRET™

glecaprevir/pibrentasvir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
oral	glecaprevir/pibrentasvir tablet 100/40 mg	lactose monohydrate
For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.		

INDICATIONS AND CLINICAL USE

MAVIRET is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not both classes of inhibitors (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

The following point should be considered when initiating treatment with MAVIRET:

MAVIRET treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Geriatrics (> 65 years of age)

In clinical studies of MAVIRET, 328 patients were age 65 and over and 47 were age 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the geriatric and younger patients (see **DOSAGE AND ADMINISTRATION, Special Populations, Geriatrics [> 65 years of age]**).

Pediatrics (< 18 years of age)

The safety and efficacy of MAVIRET in patients less than 18 years of age have not been established.

CONTRAINDICATIONS

- In patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

- In patients with severe hepatic impairment (Child-Pugh C) as the safety and efficacy have not been established (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**, **Hepatic Impairment**).

Table 1. Drugs that Are Contraindicated with MAVIRET

Drug Class/Drug Name	Effect on Concentration	Mechanism of Action	Clinical Comment
ANTICOAGULANTS			
dabigatran etexilate	↑ dabigatran	Inhibition of P-gp by MAVIRET	Coadministration with MAVIRET increased dabigatran concentrations and may increase the risk of bleeding.
ANTIMYCOBACTERIAL			
rifampin	↓ glecaprevir ↓ pibrentasvir	Induction of P-gp, BCRP, and CYP3A by rifampin	Coadministration may significantly decrease concentrations of glecaprevir and pibrentasvir, and lead to loss of therapeutic effect of MAVIRET.
ANTIVIRAL			
atazanavir	↑ glecaprevir ↑ pibrentasvir	Unknown	Risk of ALT elevations when coadministered with MAVIRET.
ETHINYL ESTRADIOL-CONTAINING PRODUCTS			
ethinyl estradiol	↑ ethinyl estradiol	Unknown	Risk of ALT elevations when coadministered with MAVIRET.
HMG-CoA REDUCTASE INHIBITORS			
atorvastatin	↑ atorvastatin	Inhibition of OATP1B1/3, BCRP, P-gp and CYP3A by MAVIRET	Coadministration with MAVIRET increased atorvastatin concentrations and may increase the potential for statin-related myopathy including rhabdomyolysis.
simvastatin	↑ simvastatin	Inhibition of OATP1B1/3 by MAVIRET	Coadministration with MAVIRET increased simvastatin concentrations and may increase the potential for statin-related myopathy including rhabdomyolysis.

See the **DRUG INTERACTION** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Potential for Hepatitis B virus (HBV) reactivation: Screen all patients for evidence of current or prior HBV infection before initiating MAVIRET therapy. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct-acting HCV antivirals (DAAs) in patients co-infected with HBV. (See **WARNINGS AND PRECAUTIONS**, **Risk of Hepatitis B Virus Reactivation**)

General

MAVIRET should not be co-administered with other medicinal products containing NS3/4A protease and NS5A inhibitors.

The number of patients infected with GT-5 and GT-6 were limited.

Use with Potent P-gp and CYP3A4 Inducers

Medicinal products that are potent P-glycoprotein (P-gp) and CYP3A4 inducers (e.g. carbamazepine, efavirenz, St. John's Wort, phenobarbital, and phenytoin) significantly decrease the plasma concentration of glecaprevir and pibrentasvir, which may lead to reduced therapeutic effect of MAVIRET or loss of virologic response. These drugs are not recommended with MAVIRET (see **DRUG INTERACTIONS**).

Hepatic/Biliary/Pancreatic

Hepatic Impairment

MAVIRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B). MAVIRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see **CONTRAINDICATIONS**).

Risk of Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV–coinfected patients who were undergoing, or completed treatment with DAA. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patients with serologic evidence of resolved HBV infection (i.e. HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage

potential for HBV reactivation (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests in Patients Coinfected with HBV**).

Liver Transplant Patients

The safety and efficacy of MAVIRET in post-liver transplant patients have not been established.

Sexual Function/Reproduction

No human data on the effect of glecaprevir and/or pibrentasvir on fertility are available. Animal studies do not indicate harmful effects of glecaprevir or pibrentasvir on fertility at exposures higher than the exposures in humans at the recommended dose (see **NON-CLINICAL TOXICOLOGY**).

Lactose Intolerance

MAVIRET contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption).

Special Populations

HCV/HBV Co-infection

The safety and efficacy of MAVIRET have not been established in HCV patients co-infected with HBV.

HCV/HIV Co-infection

The safety and efficacy of MAVIRET has not been fully established in HCV patients co-infected with Human Immunodeficiency Virus (HIV) (see **CLINICAL TRIALS**).

Pregnant Women

Pregnancy should be avoided while taking MAVIRET as there are no data on the use of MAVIRET in pregnant women. As a precautionary measure, MAVIRET use is not recommended in pregnancy unless the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their health care provider immediately in the event of a pregnancy.

In animal reproduction studies, no adverse developmental effects were observed when the components of MAVIRET were administered separately during organogenesis at exposures up to 53 and 0.07 times (rats and rabbits, respectively; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) higher than the human exposures at the recommended dose of MAVIRET. Maternal toxicity in the rabbit precluded evaluation of glecaprevir at clinical exposures. There were no effects with either compound in rodent peri/postnatal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were

approximately 47 and 74 times higher, respectively, than the exposure in humans at the recommended dose.

Nursing Women

It is unknown whether glecaprevir or pibrentasvir are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of glecaprevir and pibrentasvir in milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from MAVIRET therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Patients Treated with Vitamin K Antagonist

As liver function may change during treatment with MAVIRET, a close monitoring of International Normalised Ratio (INR) is recommended.

Monitoring and Laboratory Tests in Patients Coinfected with HBV

Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV coinfected. Co-infected patients with HBV should be monitored for clinical and laboratory signs (e.g. HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS**, **Risk of Hepatitis B Virus Reactivation**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety assessment for MAVIRET in patients with compensated liver disease (with or without cirrhosis) were derived from pooled Phase 2 and 3 studies which evaluated approximately 2,300 patients infected with genotype 1, 2, 3, 4, 5, or 6 HCV who received MAVIRET for 8, 12 or 16 weeks.

MAVIRET was generally well-tolerated and the overall proportion of patients who permanently discontinued treatment due to adverse reactions was 0.1% for patients who received MAVIRET.

Across the Phase 2 and 3 clinical studies, the most common (occurring in at least 10% of patients) adverse reactions (adverse events assessed as possibly related by the investigator) were headache and fatigue in patients treated with MAVIRET for 8, 12 or 16 weeks.

There were no differences in the overall safety for patients receiving MAVIRET for 8, 12 or 16 weeks. The type and severity of adverse reactions in patients with cirrhosis were comparable to those seen in patients without cirrhosis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions observed in greater than or equal to 3% of patients receiving 8, 12, or 16 weeks of treatment with MAVIRET are presented in **Table 2**. The most common adverse reactions were headache and fatigue in patients treated with MAVIRET overall. In patients receiving MAVIRET who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1), 19% had an adverse reaction of moderate severity (Grade 2), <1% had an adverse reaction of severe severity (Grade 3), and no subject had a Grade 4 or 5 adverse reaction. In the placebo-controlled study (ENDURANCE-2), these adverse reactions occurred at a similar frequency in patients treated with placebo compared to patients treated with MAVIRET. In the active-controlled study (ENDURANCE-3), adverse reactions occurred at a similar frequency in patients treated with sofosbuvir and daclatasvir for 12 weeks compared to patients treated with MAVIRET for 12 weeks. The rate of discontinuation due to ADRs was similar for MAVIRET (1.3%) and for sofosbuvir and daclatasvir (0.9%).

Table 2. Adverse Reactions (All Grades) Observed in ≥ 3.0% of the Patients in Phase 2, 3 Clinical Studies.

SOC Preferred Term	MAVIRET[a] GT-1, -2, -4, -5 - 6 8, 12 weeks N=1,520 n (%)	MAVIRET[b] GT-3 8, 12, 16 weeks N=632 n (%)	MAVIRET[c] PI or NS5A-I Experienced 12, 16 weeks N=113 n (%)	MAVIRET[d] Overall N=2,265 n (%)
Nervous System Disorders				
Headache	171 (11.3)	106 (16.8)	21 (18.6)	298 (13.2)
General Disorders and Administration Site Conditions				
Fatigue	158 (10.4)	92 (14.6)	9 (8.0)	259 (11.4)
Gastrointestinal Disorders				
Nausea	105 (6.9)	57 (9.0)	10 (8.8)	172 (7.6)
Diarrhea	44 (2.9)	38 (6.0)	4 (3.5)	86 (3.8)
Skin and Subcutaneous Tissue Disorders				
Pruritus	61 (4.0)	12 (3.0)	2 (1.8)	75 (3.3)

a. ADRs observed in registrational clinical studies (M14-867, M14-868, M13-590, M15-464, M15-172, M13-583) for GT-1, -2, -4, -5 or -6 with or without compensated cirrhosis.

b. ADRs observed in registrational studies M14-868 and M13-594 for GT-3 with or without compensated cirrhosis.

c. ADRs observed in registrational study M15-410 for PI and/or NS5A-I experienced patients with or without cirrhosis with GT-1 or -4.

d. Total ADRs observed across all groups TN, TE-PRS or PI and/or NS5A-I experienced and GT1 to 6 with or without cirrhosis.

Adverse Reactions in Patients with Severe Renal Impairment Including Patients on Dialysis

The safety of MAVIRET in patients with chronic kidney disease (Stage 4 or Stage 5 including patients on dialysis) and genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection with compensated liver disease (with or without cirrhosis) was assessed in 104 patients (EXPEDITION-4). The most common adverse reactions were pruritus and fatigue in patients treated with MAVIRET for 12 weeks. Adverse reactions observed in greater than or equal to 3% of patients receiving 12 weeks of treatment with MAVIRET are presented in **Table 3**. In patients treated with MAVIRET who reported an adverse reaction, 55% had adverse reactions of mild severity, 35% had a severity of Grade 2, and 10% had a severity of Grade 3. No patients experienced a serious adverse reaction. The proportion of patients who permanently discontinued treatment due to adverse reactions was 1.9%.

Table 3. Adverse Reactions (All Grades) Observed in ≥ 3% of the Patients with Severe Renal Impairment Including Patients on Dialysis (EXPEDITION-4)

SOC Preferred Term	MAVIRET 12 weeks N = 104
Skin and Subcutaneous Tissue Disorders	
Pruritus	17.3%
General Disorders and Administration Site Conditions	
Fatigue	11.5%
Asthenia	6.7%
Gastrointestinal Disorders	
Nausea	8.7%
Diarrhea	3.8%
Gastroesophageal Reflux Disease	3.8%
Nervous System Disorders	
Headache	5.8%
Dizziness	3.8%
Psychiatric Disorders	
Insomnia	3.8%

Abnormal Hematological and Clinical Chemistry Findings

Serum Bilirubin Elevations

Elevations in total bilirubin of at least 2x ULN were observed in 1% of subjects related to glecaprevir-mediated inhibition of bilirubin transporters and metabolism. Bilirubin elevations

were asymptomatic, transient, and typically occurred early during treatment. Bilirubin elevations were predominantly indirect, mostly in patients with pre-existing elevated bilirubin (consistent with Gilbert's Syndrome), and not associated with ALT elevations.

Post-Market Adverse Drug Reactions

The post-marketing adverse drug reactions are not yet available for MAVIRET.

DRUG INTERACTIONS

Drug-Drug Interactions

All drug-drug interaction studies were performed with the glecaprevir and pibrentasvir combination in non-HCV infected subjects.

Potential for MAVIRET to Affect Other Drugs

Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Coadministration with MAVIRET may increase plasma concentration of drugs that are substrates of P-gp, BCRP, OATP1B1 or OATP1B3. Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1. Significant interactions are not expected when MAVIRET is coadministered with substrates of CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2D6, UGT1A1, or UGT1A4.

Potential for Other Drugs to Affect MAVIRET

Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Co-administration of MAVIRET with medicinal products that inhibit P-gp and BCRP expressed in the intestine is unlikely to affect glecaprevir or pibrentasvir concentrations, but inhibition of P-gp and BCRP in the liver may slow elimination of glecaprevir and pibrentasvir. Medicinal products that inhibit OATP1B1/3 may increase systemic concentrations of glecaprevir, but total liver exposure of glecaprevir is unaffected.

Coadministration of MAVIRET with drugs that are strong inducers of P-gp/CYP3A may significantly decrease glecaprevir and pibrentasvir plasma concentrations (see **WARNINGS AND PRECAUTIONS**).

Table 4 provides the effect of coadministration of MAVIRET on concentrations of concomitant drugs and the effect of concomitant drugs on glecaprevir and pibrentasvir. Coadministration of MAVIRET with atorvastatin, atazanavir, dabigatran etexilate, ethinyl estradiol-containing products, rifampin and simvastatin are contraindicated (see also **CONTRAINDICATIONS**).

Table 4. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a,b]	Clinical Comments
ANTIARRHYTMICS		
digoxin	↑ digoxin	Concomitant administration of MAVIRET with digoxin leads to increases in the concentration of digoxin. Caution is warranted and a 50% dose reduction of digoxin is recommended when coadministered with MAVIRET.
ANTICONVULSANTS		
carbamazepine	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
HERBAL PRODUCTS		
St. John's Wort (*Hypericum perforatum*)	↓ glecaprevir ↓ pibrentasvir	It is expected that coadministration may lead to reduced therapeutic effect of MAVIRET and is not recommended.
HCV-ANTIVIRAL AGENTS		
sofosbuvir	↑ sofosbuvir ↔ GS-331007	Coadministration with MAVIRET increases sofosbuvir concentrations, but does not affect GS-331007. No dose adjustment is required.
HIV-ANTIVIRAL AGENTS		
darunavir + ritonavir lopinavir/ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration with MAVIRET significantly increased glecaprevir and pibrentasvir concentrations and is not recommended.
efavirenz[c]	↓ glecaprevir ↓ pibrentasvir	Coadministration with efavirenz containing regimens may lead to reduced therapeutic effect of MAVIRET and is not recommended.
rilpivirine	↑ rilpivirine	Coadministration with MAVIRET may lead to increased rilpivirine exposure but no dose adjustment is necessary. Caution should be used when these drugs are coadministered (see rilpivirine Product Monograph).
tenofovir alafenamide[d]	↔tenofovir	No dose adjustment is required.
tenofovir disoproxil fumarate[c]	↑ tenofovir	No dose adjustment is required.
HMG-COA REDUCTASE INHIBITORS		
lovastatin pravastatin rosuvastatin	↑ lovastatin ↑ pravastatin ↑ rosuvastatin	Coadministration with MAVIRET may increase the concentration of HMG-CoA reductase inhibitors which is associated with myopathy, including rhabdomyolysis. Coadministration of lovastatin with the MAVIRET is not recommended. Pravastatin dose should be reduced by 50% when co-

		administered with MAVIRET. Coadministration of rosuvastatin at a dose not exceeding 5 mg may be used with MAVIRET
IMMUNOSUPPRESSANTS		
cyclosporine	↑ glecaprevir ↑ pibrentasvir	MAVIRET is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day. Cyclosporine concentrations are not affected by MAVIRET.
tacrolimus	↑ tacrolimus	The combination of MAVIRET with tacrolimus should be used with caution. Increase of tacrolimus exposure is expected. Therefore, therapeutic drug monitoring of tacrolimus is recommended and a dose adjustment of tacrolimus made accordingly.
PROTON PUMP INHIBITORS		
omeprazole	↓ glecaprevir ↔ pibrentasvir	Increased gastric pH may reduce absorption of glecaprevir, but is not expected to have a clinically significant effect on the efficacy of MAVIRET. No dose adjustment is required.
VITAMIN K ANTAGONISTS		
vitamin K antagonists	Not studied	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with MAVIRET.

↑= increase; ↓= decrease; ↔= no effect

See also **DRUG INTERACTIONS Table 5** and **Table 6.**

a. Digoxin, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, lovastatin, pravastatin, rosuvastatin, rilpivirine, sofosbuvir, and tacrolimus did not lead to clinically significant changes in glecaprevir or pibrentasvir concentrations when coadministered with MAVIRET.

b. Coadministration with MAVIRET did not lead to clinically significant changes in carbamazepine, cobicistat, cyclosporine, darunavir, efavirenz, elvitegravir, emtricitabine, lopinavir, omeprazole or ritonavir, concentrations.

c. Interaction studied with the efavirenz/emtricitabine/tenofovir disoproxil fumarate combination.

d. Interaction studied with the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide combination.

Assessment of Drug Interactions

Drugs without Clinically Significant Interactions with MAVIRET

No dose adjustment is required when MAVIRET is coadministered with the following medications: abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/cobicistat, emtricitabine, felodipine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, omeprazole, raltegravir, sofosbuvir, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.

Pharmacokinetic Parameters for Clinically Relevant Drug Interactions

Drug interaction studies were performed with glecaprevir/pibrentasvir and other drugs that are likely to be coadministered and with drugs commonly used as probes for pharmacokinetic interactions. **Table 5** and **Table 6** summarize the pharmacokinetic effects when glecaprevir/pibrentasvir was coadministered with other drugs which showed potentially clinically relevant changes.

Table 5. Drug Interactions: Changes in Pharmacokinetic Parameters of Glecaprevir (GLE) or Pibrentasvir (PIB) in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	DAA	Central Value Ratio (90% CI)		
					C_{max}	AUC	C_{min}
ANTICONVULSANTS							
carbamazepine	200 twice daily	300/120 single dose	10	GLE	0.33 (0.27, 0.41)	0.34 (0.28, 0.40)	--
				PIB	0.50 (0.42, 0.59)	0.49 (0.43, 0.55)	--
ANTIMYCOBACTERIAL							
rifampin	600 (first dose)	300/120 single dose	12	GLE	6.52 (5.06, 8.41)	8.55 (7.01, 10.4)	--
				PIB	↔	↔	--
	600 once daily	300/120 single dose[a]	12	GLE	0.14 (0.11, 0.19)	0.12 (0.09, 0.15)	--
				PIB	0.17 (0.14, 0.20)	0.13 (0.11, 0.15)	--
HIV-ANTIVIRAL AGENTS							
atazanavir (ATZ) + ritonavir (rtv)	ATZ 300 + rtv 300 once daily	300/120 once daily[b]	12	GLE	≥4.06 (3.15, 5.23)	≥6.53 (5.24, 8.14)	≥14.3 (9.85, 20.7)
				PIB	≥1.29 (1.15, 1.45)	≥1.64 (1.48, 1.82)	≥2.29 (1.95, 2.68)
darunavir (DRV) + rtv	DRV 800 + rtv 100 once daily	300/120 once daily	8	GLE	3.09 (2.26, 4.20)	4.97 (3.62, 6.84)	8.24 (4.40, 15.4)
				PIB	↔	↔	1.66 (1.25, 2.21)
lopinavir (LPV)/rtv	LPV 400 + rtv 100 twice daily	300/120 once daily	9	GLE	2.55 (1.84, 3.52)	4.38 (3.02, 6.36)	18.6 (10.4, 33.5)
				PIB	1.40 (1.17, 1.67)	2.46 (2.07, 2.92)	5.24 (4.18, 6.58)
IMMUNOSUPPRESSANTS							
cyclosporine	100 single dose	300/120 once daily	12	GLE	1.30 (0.95, 1.78)	1.37 (1.13, 1.66)	1.34 (1.12, 1.60)
				PIB	↔	↔	1.26 (1.15, 1.37)
	400 single	300/120	11	GLE	4.51	5.08	--

Co-administered Drug	Regimen of Co-administered Drug (mg)	Regimen of GLE/PIB (mg)	N	DAA	Central Value Ratio (90% CI)		
					C_{max}	AUC	C_{min}
	dose	single dose			(3.63, 6.05)	(4.11, 6.29)	
				PIB	↔	1.93 (1.78, 2.09)	--
PROTON PUMP INHIBITORS							
omeprazole	20 once daily	300/120 single dose	9	GLE	0.78 (0.60, 1.00)	0.71 (0.58, 0.86)	--
				PIB	↔	↔	--
	40 once daily	300/120 single dose	12	GLE	0.36 (0.21, 0.59)	0.49 (0.35, 0.68)	--
				PIB	↔	↔	--

DAA=direct acting antiviral

↔ = No change (central value ratio 0.80 to 1.25)

a. Effect of rifampin on glecaprevir and pibrentasvir 24 hours after final rifampin dose.

b. Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.

Table 6. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Combination of Glecaprevir/Pibrentasvir (GLE/PIB)

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of GLE/PIB (mg)	N	Central Value Ratio (90% CI)		
				C_{max}	AUC	C_{min}
ANTIARRHYTHMICS						
digoxin	0.5 single dose	400/120 once daily	12	1.72 (1.45, 2.04)	1.48 (1.40, 1.57)	--
ANTICOAGULANTS						
dabigatran etexilate	dabigatran etexilate 150 single dose	300/120 once daily	11	2.05 (1.72, 2.44)	2.38 (2.11, 2.70)	--
CONTRACEPTIVES						
ethinyl estradiol (EE)	EE/norgestimate 35 mcg/ 250 mcg once daily	300/120 once daily	11	1.31 (1.24, 1.38)	1.28 (1.23, 1.32)	1.38 (1.25, 1.52)
norgestrel				1.54 (1.34, 1.76)	1.63 (1.50, 1.76)	1.75 (1.62, 1.89)
norgestromin				↔	1.44 (1.34, 1.54)	1.45 (1.33, 1.58)
ethinyl estradiol	EE/levonorgestrel 20 mcg/ 100 mcg once daily	300/120 once daily	12	1.30 (1.18, 1.44)	1.40 (1.33, 1.48)	1.56 (1.41, 1.72)
norgestrel				1.37 (1.23, 1.52)	1.68 (1.57, 1.80)	1.77 (1.58, 1.98)
HCV-ANTIVIRAL AGENTS						
sofosbuvir	sofosbuvir 400 once daily	400/120 mg once daily	8	1.66 (1.23, 2.22)	2.25 (1.86, 2.72)	--
GS-331007 (metabolite)			8	↔	↔	1.85 (1.67, 2.04)
HIV-ANTIVIRAL AGENTS						
rilpivirine	25 once daily	300/120 once daily	12	2.05 (1.73, 2.43)	1.84 (1.72, 1.98)	1.77 (1.59, 1.96)
tenofovir alafenamide (TAF)	EVG/COBI/ FTC/TAF 150/150/ 200/10 once daily	300/120 once daily	11	↔	↔	↔
tenofovir disoproxil fumarate (TDF)	EFV/FTC/ TDF 600/200 /300 once	300/120 once daily	12	↔	1.29 (1.23, 1.35)	1.38 (1.31, 1.46)

Coadministered Drug	Regimen of Coadministered Drug (mg)	Regimen of GLE/PIB (mg)	N	Central Value Ratio (90% CI)		
				C_{max}	AUC	C_{min}
	daily					
HMG CoA REDUCTASE INHIBITORS						
atorvastatin	10 once daily	400/120 once daily	11	22.0 (16.4, 29.5)	8.28 (6.06, 11.3)	--
lovastatin	10 once daily	300/120 once daily	12	↔	1.70 (1.40, 2.06)	--
lovastatin acid (metabolite)				5.73 (4.65, 7.07)	4.10 (3.45, 4.87)	--
pravastatin	10 once daily	400/120 once daily	12	2.23 (1.87, 2.65)	2.30 (1.91, 2.76)	--
rosuvastatin	5 once daily	400/120 once daily	11	5.62 (4.80, 6.59)	2.15 (1.88, 2.46)	--
simvastatin	5 once daily	300/120 once daily	12	1.99 (1.60, 2.48)	2.32 (1.93, 2.79)	--
simvastatin acid (metabolite)				10.7 (7.88, 14.6)	4.48 (3.11, 6.46)	--
IMMUNOSUPPRESSANTS						
tacrolimus	1 single dose	300/120 once daily	10	1.50 (1.24, 1.82)	1.45 (1.24, 1.70)	--

↔ = No change (central value ratio 0.80 to 1.25) COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine

Drug-Food Interactions

Food increases the bioavailability of MAVIRET (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Drug-Herb Interactions

Coadministration of St. John's Wort *(Hypericum perforatum)*, may lead to reduced therapeutic effect of MAVIRET and is not recommended (see **DRUG INTERACTIONS, Table 4**).

Drug-Laboratory Interactions

Interactions of MAVIRET with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- MAVIRET is glecaprevir and pibrentasvir fixed-dose combination tablets.
- Treatment durations depend on HCV genotype, cirrhosis status, and treatment history.
- Screen all patients for evidence of current or prior HBV infection by measuring HbsAg and anti-HBc before initiating treatment for HCV with MAVIRET (see **WARNINGS AND PRECAUTIONS**).
- MAVIRET tablets should be swallowed whole and not chewed, crushed, or broken.

Recommended Dose and Dosage Adjustment

The recommended oral dose of MAVIRET is three fixed-dose combination glecaprevir/pibrentasvir 100/40 mg tablets administered once daily with food without regard to fat or calorie content (see **ACTION AND CLINICAL PHARMACOLOGY**). No dose adjustment is possible.

Table 7 and **Table 8** provide the recommended MAVIRET treatment duration based on the patient population in HCV mono-infected and HCV/HIV-1 co-infected patients with compensated liver disease (with or without cirrhosis) and with or without renal impairment including patients receiving dialysis.

Table 7. Recommended MAVIRET Treatment Duration for Treatment-Naive Patients Infected by Genotypes 1 to 6

HCV Genotype	Treatment Duration	
	Without Cirrhosis	With Cirrhosis
GT-1, -2, -3, -4, -5 or -6	8 Weeks	12 Weeks

GT= genotype

Table 8. Recommended MAVIRET Treatment Duration for Treatment-Experienced Patients Infected by Genotypes 1 to 6

HCV Genotype	Treatment History	Treatment Duration	
		Without Cirrhosis	With Cirrhosis
GT-1, -2, -4, -5, or -6	PRS[a]	8 Weeks	12 Weeks
GT-1	NS3/4A PI[b] (NS5A inhibitor-naïve)	12 Weeks	
GT-1	NS5A[c] (NS3/4A inhibitor-naïve)	16 Weeks	
GT-3	PRS[a]	16 Weeks	

GT = genotype; PI = protease inhibitor; PR = peginterferon/ribavirin; PRS = peginterferon/ribavirin + sofosbuvir; SMV = simeprevir; TRV = telapevir; BOC = boceprevir; DCV = daclatasvir; LDV = ledipasvir; SOF = sofosbuvir.

a. Experienced with regimens containing interferon, peginterferon, ribavirin, and/or sofosbuvir (PR, SOF + PR, SOF + R), but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

b. Experienced with regimens containing SMV + SOF or SMV + PR or BOC + PR or TPV + PR.

c. Experienced with regimens containing DCV + SOF, DCV + PR, or LDV + SOF.

Special Populations

Pediatrics (< 18 years of age)

The safety and efficacy of MAVIRET in patients less than 18 years of age have not been established.

Geriatrics (> 65 years of age)

No dose adjustment of MAVIRET is required in geriatric patients.

Gender/Weight

No dose adjustment of MAVIRET is necessary based on gender or weight.

Race/Ethnicity

No dose adjustment of MAVIRET is necessary based on race or ethnicity.

Hepatic Impairment

No dose adjustment of MAVIRET is required in patients with mild hepatic impairment (Child-Pugh A). MAVIRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see **CONTRAINDICATIONS** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment**).

Renal Impairment

No dose adjustment of MAVIRET is required in patients with any degree of renal impairment including patients on dialysis (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Renal Impairment**).

Missed Dose

Patients should be informed that in case a dose is missed, the prescribed dose can be taken within 18 hours of the scheduled time for the dose that was missed.

If more than 18 hours has passed since the dose is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The highest documented doses administered to healthy volunteers is 1200 mg once daily for 7 days for glecaprevir and 600 mg once daily for 10 days for pibrentasvir. In case of overdose, the patient should be monitored for any signs and symptoms of toxicities. Appropriate symptomatic treatment should be instituted immediately. Glecaprevir and pibrentasvir were not significantly removed by hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MAVIRET is a fixed-dose combination of two pangenotypic, direct-acting antiviral agents, glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle (see **MICROBIOLOGY**).

Pharmacodynamics

Effects on Electrocardiogram

The effect of glecaprevir (up to 600 mg) in combination with pibrentasvir (up to 240 mg) on QTc interval was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT study. At 20-fold of glecaprevir and 5-fold of pibrentasvir therapeutic concentrations, the glecaprevir and pibrentasvir combination does not prolong the QTc interval.

Pharmacokinetics

Based on the population pharmacokinetic analysis, the median steady-state pharmacokinetic parameters of glecaprevir and pibrentasvir in HCV infected patients and healthy subjects are provided in **Table 9**.

Table 9. Pharmacokinetics of Multiple Doses of Glecaprevir 300 mg Once Daily and Pibrentasvir 120 mg Once Daily in HCV-Infected Patients and Healthy Subjects

Direct Acting Antivirals (DAAs)	Pharmacokinetic Parameters	Healthy Subjects (N=230)[a]	HCV Infected Patients[b]	
			With Cirrhosis (N=280)[c]	Without Cirrhosis (N=1,804)[c]
Glecaprevir	C_{max} (ng/mL)	1,230	1,110	597
	AUC_{24} (ng·h/mL)	4,380	10,500	4,800
Pibrentasvir	C_{max} (ng/mL)	295	111	110
	AUC_{24} (ng·h/mL)	2,170	1,530	1,430

a. Overall geometric mean

b. Pharmacokinetics were similar in treatment-naïve or treatment-experienced patients

c. Geometric mean of individual-estimated AUC24

Absorption

Following single-dose administration of glecaprevir and pibrentasvir in healthy subjects, peak plasma concentrations were observed at 5.0 hours (glecaprevir) and 5.0 hours (pibrentasvir) post-dose.

Effects of Food on Oral Absorption

There were increases in glecaprevir AUC_T and C_{max} when a single 300 mg/120 mg dose of MAVIRET was administered under moderate fat, moderate calorie fed conditions (approximately 142% and 210%, respectively) and high fat, high calorie fed conditions (approximately 67% and 88%, respectively) when compared to administration under fasting conditions.

Similarly, there were increases in pibrentasvir AUC_T and C_{max} when a single 300 mg/120 mg dose of MAVIRET was administered under moderate fat, moderate calorie fed conditions (approximately 27% and 71%, respectively) and high fat, high calorie fed conditions (approximately 42% and 87%, respectively) when compared to administration under fasting conditions.

In Phase 2 and 3 registrational studies, glecaprevir and pibrentasvir were administered with food without regard to fat and calorie content.

Distribution

Glecaprevir and pibrentasvir are highly bound to plasma proteins (97.5% and > 99.9%, respectively). Ex vivo blood to plasma ratios were 0.57 (glecaprevir) and 0.62 (pibrentasvir).

Metabolism

Only unchanged glecaprevir and pibrentasvir were detected in plasma. Several oxidative metabolites (26% of dose) of glecaprevir were identified in feces. Metabolism by CYP3A plays a secondary role in the disposition of glecaprevir. Pibrentasvir was not metabolized and was recovered in feces only as unchanged parent drug.

Elimination

Glecaprevir and pibrentasvir are primarily eliminated through the biliary-fecal route. Mean half-lives of 6 hours (glecaprevir) and 13 hours (pibrentasvir) were observed when coadministered in healthy subjects. Following a single dose of [^{14}C]glecaprevir, 92.1% of the radioactive dose was recovered in feces and 0.7% was recovered in urine. Following a single dose of [^{14}C] pibrentasvir, 96.6% of the radioactive dose was recovered in feces and none was recovered in urine.

Special Populations and Conditions

Pediatrics (< 18 years of age)

The pharmacokinetics of MAVIRET in pediatric patients have not been established (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pediatrics (< 18 years of age)**).

Geriatrics (≥ 65 years of age)

Within the age range (18 to 88 years) analyzed, age did not have a clinically relevant effect on exposure of glecaprevir or pibrentasvir.

Gender/Weight

Sex and body weight did not have a clinically relevant effect on exposure of glecaprevir or pibrentasvir.

Race/Ethnicity

Race or ethnicity did not have a clinically relevant effect on exposure of glecaprevir or pibrentasvir.

Hepatic Impairment

Hepatic impairment studies were conducted with a single dose of the glecaprevir 300 mg and pibrentasvir 120 mg combination in HCV-negative subjects under non-fasting conditions. Compared to subjects with normal hepatic function, glecaprevir exposures were higher in subjects with Child-Pugh A (↑ 33% AUC), Child-Pugh B (↑ 38% C_{max}, ↑ 2-fold AUC), and Child-Pugh C (↑ 5-fold C_{max}, ↑ 11-fold AUC) hepatic impairment. Pibrentasvir exposures were similar in subjects with Child-Pugh A (≤20% difference in C_{max} or AUC), but higher in subjects

with Child-Pugh B (↑ 26% C_{max} and AUC) and Child-Pugh C (↓ 41% C_{max}, ↑ 2-fold AUC) hepatic impairment.

Population pharmacokinetic analysis demonstrated that following administration of MAVIRET in HCV infected patients with compensated cirrhosis, exposure of glecaprevir was approximately 2-fold and pibrentasvir exposure was similar to non-cirrhotic HCV infected patients (see also **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Renal Impairment

Renal impairment studies were conducted with a single dose of the glecaprevir 300 mg and pibrentasvir 120 mg combination in HCV-negative subjects with mild (eGFR 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), or ESRD not on dialysis (eGFR < 15 mL/min/1.73 m^2). Compared to subjects with normal renal function, glecaprevir AUC values were similar in subjects with mild renal impairment (13% difference), but higher in subjects with moderate renal impairment (↑30%), severe renal impairment (↑ 45%), or ESRD not on dialysis (↑ 56%). Compared to subjects with normal renal function, pibrentasvir AUC values were similar in subjects with mild (11% difference) or moderate (25% difference) renal impairment, but higher in subjects with severe renal impairment (↑ 37%), or ESRD not on dialysis (↑ 46%). C_{max} values were similar across all groups for glecaprevir (≤ 9% difference) and pibrentasvir (≤ 25% difference).

The glecaprevir 300 mg and pibrentasvir 120 mg combination was also administered to subjects requiring dialysis 3 hours before the start of hemodialysis and on a non-dialysis day. Exposures were similar for glecaprevir (≤ 7% difference in C_{max} or AUC) and pibrentasvir (≤ 18% difference in C_{max} or AUC) when dosed before dialysis compared to the non-dialysis day.

Overall, the changes in exposures of MAVIRET in HCV-infected patients with renal impairment with or without dialysis were not considered clinically significant (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store between 2 and 30°C.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MAVIRET 100/40 mg tablets are pink-colored, film-coated, oblong biconvex shaped and debossed with “NXT” on one side.

MAVIRET is dispensed in a monthly carton. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs.

Each daily dose pack contains three 100 mg/40 mg glecaprevir/pibrentasvir tablets.

Listing of Non-Medicinal Ingredients

Each glecaprevir/pibrentasvir co-formulated immediate release tablet contains 100 mg glecaprevir /40 mg pibrentasvir with the following non-medicinal ingredients: copovidone (type K 28), vitamin E polyethylene glycol succinate, colloidal silicon dioxide, propylene glycol monocaprylate (type II), croscarmellose sodium, sodium stearyl fumarate, and film-coating (hypromellose 2910, lactose monohydrate, titanium dioxide, polyethylene glycol 3350 and iron oxide red).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

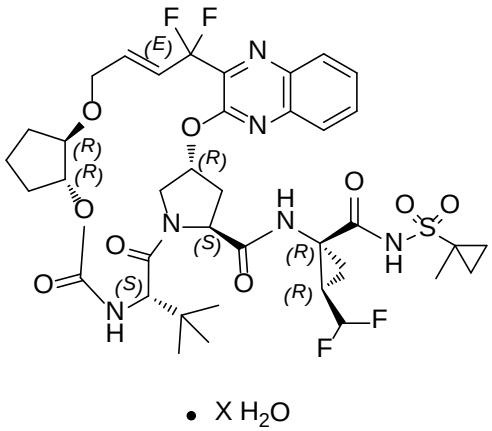
Glecaprevir

Common name: glecaprevir

Chemical name: (3a*R*,7*S*,10*S*,12*R*,21*E*,24a*R*)-7-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1*H*,10*H*-9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12-*b*]quinoxaline-10-carboxamide hydrate

Molecular formula and molecular mass: $C_{38}H_{46}F_4N_6O_9S$ (anhydrate) 838.87 g/mol (anhydrate)

Structural formula:

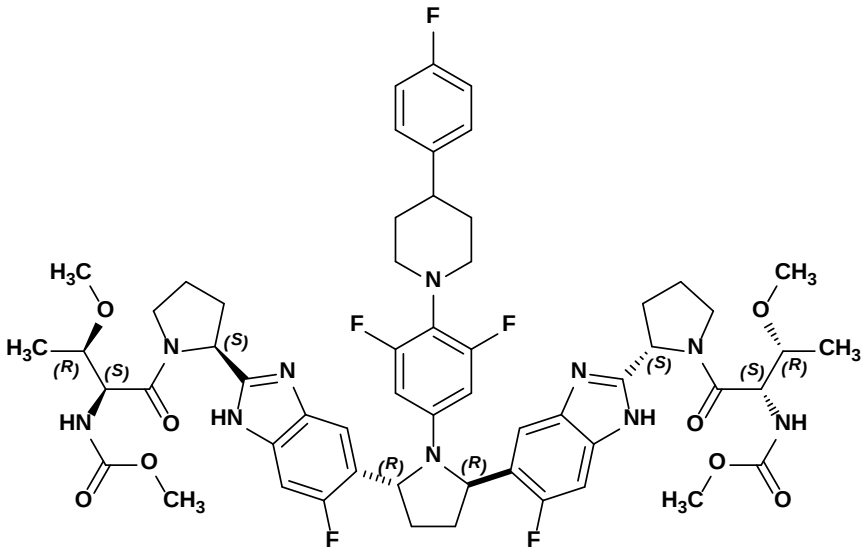


Physicochemical properties:

Appearance: Glecaprevir is a white to off-white powder.

Solubility: Glecaprevir has a solubility of less than 0.1 to 0.3 mg/mL across a pH range of 2–7 at 37ºC and is practically insoluble in water, but is sparingly soluble in ethanol.

Pibrentasvir

Common name:	pibrentasvir
Chemical name:	Methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate
Molecular formula and molecular mass:	$C_{57}H_{65}F_5N_{10}O_8$ 1113.18 g/mol
Structural formula:	

Physicochemical properties:

Appearance	Pibrentasvir is a white to off-white to light yellow powder.
Solubility	Pibrentasvir has a solubility of less than 0.1 mg/mL across a pH range of 1–7 at 37°C and is practically insoluble in water, but is freely soluble in ethanol.

CLINICAL TRIALS

Trial Design

The efficacy and safety of MAVIRET was evaluated in nine Phase 2-3 clinical trials, in over 2,300 patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection and with compensated liver disease (with or without cirrhosis), as summarized in **Table 10**.

Table 10. Clinical Studies Conducted with MAVIRET in Patients with HCV Genotype 1, 2, 3, 4, 5 or 6 Infection

HCV Genotype (GT)	Study #	Number of Patients Treated N (regimen)	Trial Design	Dosage, Route of Administration and Duration
TN and TE patients without cirrhosis				
GT-1	ENDURANCE-1 (M13-590)	351 (8 weeks) 352 (12 weeks)	Randomized (1:1) and open-label study	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks
	SURVEYOR-1 (M14-867)	34	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 weeks
GT-2	ENDURANCE-2 (M15-464)	202 (12 weeks) 100 (Placebo)	Randomized (2:1), placebo-controlled	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
	SURVEYOR-2 (M14-868)	199 (8 weeks) 25 (12 weeks)	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks
GT-3	ENDURANCE-3 (M13-594)	157 (8 weeks) 233 (12 weeks) 115 (Sofosbuvir + daclatasvir 12 weeks)	Partially-randomized, open-label, active-controlled (all TN patients)	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 weeks
	SURVEYOR-2 (M14-868)	29 TN only (8 weeks) 76 (12 weeks) 22 TE only (16 weeks)	Partially Randomized, Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 or 12 or 16 weeks
GT-4, -5, -6	ENDURANCE-4 (M13-583)	121	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
	SURVEYOR-1 (M14-867)	32	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks

	SURVEYOR-2 (M14-868)	58	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 8 weeks
TN and TE patients with cirrhosis				
GT-1, -2, -4, -5, -6	EXPEDITION-1 (M14-172)	146	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
GT-3	SURVEYOR-2 (M14-868)	64 TN only (12 weeks) 51 TE only (16 weeks)	Open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 or 16 weeks
Patients with CKD stage 4 and 5 with or without cirrhosis				
GT-1to -6	EXPEDITION-4 (M15-462)	104	Single-arm, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 weeks
NS5A and/or PI-experienced patients with or without cirrhosis				
GT-1, -4	MAGELLAN-1 (M15-410)	66 (12 weeks) 47 (16 weeks)	Randomized, multipart, open-label	glecaprevir/pibrentasvir tablet: 300/120 mg QD Oral 12 or 16 weeks

TN = treatment-naïve, TE = treatment-experienced (includes previous treatment that included pegylated interferon (or interferon), and/or ribavirin and/or sofosbuvir), PI = Protease Inhibitor, CKD = chronic kidney disease, QD = once daily

Serum HCV RNA values were measured during the clinical studies using the Roche COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL (except for SURVEYOR-1 and SURVEYOR-2which used the Roche COBAS TaqMan real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with an LLOQ of 25 IU/mL). Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint in all the studies to determine the HCV cure rate.

Among patients in Phase 2 and 3 clinical trials who received the recommended regimen (N=1190), 97% achieved SVR (97% with cirrhosis and 97% without cirrhosis), while 0.6% experienced on treatment virologic failure and 0.9% experienced post-treatment relapse. Among the treatment naïve patients without cirrhosis (all genotypes) who received MAVIRET for 8 weeks, the SVR12 rate was 97% (639/657) with <1% (6/657) virologic failure rate.

Clinical Studies in Treatment-Naive or Treatment-Experienced-PRS Patients with or without Cirrhosis Infected with Genotypes 1, 2, 4, 5 or 6.

Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for treatment-naïve or PRS-treatment-experienced-patients with or without cirrhosis with genotype 1, 2, 4, 5, or 6 infection in ENDURANCE-1, -2, -4, SURVEYOR-1 , -2, and EXPEDITION-1 are provided in **Table 11**.

Table 11. Demographic and Other Baseline Disease Characteristics of the Population for the Treatment of HCV Genotypes 1, 2, 4, 5 or 6 (Phase 2, 3 Studies[a])

Characteristics	Genotype					Total N=1,520 n (%)
	GT-1 N=834 n (%)	GT-2 N=450 n (%)	GT-4 N=158 n (%)	GT-5 N=31 n (%)	GT-6 N=47 n (%)	
Age (years)						
< 65	724 (86.8)	345 (76.7)	141 (89.2)	19 (61.3)	42 (89.4)	1,271 (83.6)
≥ 65	110 (13.2)	105 (23.3)	17 (10.8)	12 (38.7)	5 (10.6)	249 (16.4)
Gender						
Male	420 (50.4)	226 (50.2)	101 (63.9)	17 (54.8)	26 (55.3)	790 (52.0)
Female	414 (49.6)	224 (49.8)	57 (36.1)	14 (45.2)	21 (44.7)	730 (48.0)
Race						
White	708 (84.9)	338 (75.1)	124 (78.5)	20 (64.5)	5 (10.6)	1,195 (78.6)
Black	36 (4.3)	21 (4.7)	24 (15.2)	4 (12.9)	NA	85 (5.6)
Asian	81 (9.7)	80 (17.8)	10 (6.3)	2 (6.5)	41 (87.2)	214 (14.1)
Other	9 (1.1)	11 (2.4)	NA	5 (16.1)	1 (2.1)	26 (1.7)
BMI						
< 30 kg/m^2	674 (80.8)	344 (76.4)	128 (81.0)	21 (67.7)	44 (93.6)	1,211 (79.7)
≥ 30 kg/m^2	160 (19.2)	106 (23.6)	30 (19.0)	10 (32.3)	3 (6.4)	309 (20.3)
Genotype/Subtype						
1a	377 (45.2)	NA	NA	NA	NA	377 (24.8)
1b	454 (54.4)	NA	NA	NA	NA	454 (29.9)
2	NA	450 (100)	NA	NA	NA	450 (29.6)
4	NA	NA	158 (100)	NA	NA	158 (10.4)
5 and 6	NA	NA	NA	31 (100)	47 (100)	78 (5.1)
HCV RNA Viral Load (Log_{10} IU/mL), mean (SD)	6.1 (0.68)	6.2 (0.94)	5.9 (0.67)	6.1 (0.56)	6.6 (0.83)	6.1 (0.78)
Fibrosis Stage						
F0-F2	676 (81.1)	371 (82.4)	130(82.3)	27 (87.1)	33 (70.2)	1,237 (81.4)
F3	64 (7.7)	48 (10.7)	12 (7.6)	2 (6.5)	7 (14.9)	133 (8.8)
F4	90 (10.8)	31 (6.9)	16 (10.1)	2 (6.5)	7 (14.9)	146 (9.6)
Cirrhosis						
Yes	90 (10.8)	31 (6.9)	16 (10.1)	2 (6.5)	7 (14.9)	146 (9.6)
No	744 (89.2)	419 (93.1)	142 (89.9)	29 (93.5)	40 (85.1)	1,374 (90.4)
Prior HCV Therapy						
TN	533 (63.9)	359 (79.8)	112 (70.9)	25 (80.6)	41 (87.2)	1,070 (70.4)
TE-PRS	301 (36.1)	91 (20.2)	46 (29.1)	6 (19.4)	6 (12.8)	450 (29.6)
P/R-experienced	293 (35.1)	74 (16.4)	45 (28.5)	6 (19.4)	6 (12.8)	424 (27.9)
SOF-experienced	8 (1.0)	17 (3.8)	1 (0.6)	NA	NA	26 (1.7)

a. Population includes TN or TE-PRS patients and excludes patients with severe renal impairment (Study M15-462).

BMI = body mass index; GT = genotype; P/R = peginterferon/ribavirin; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SD = standard deviation; TN = treatment-naïve; TE = treatment-experienced; SOF = sofosbuvir

Study Results

The response rates for MAVIRET in genotype 1, 2, 4, 5 or 6 infected patients who were treatment-naïve or those who previously failed regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir (PRS) treated for 8 weeks (without cirrhosis) and 12 weeks (with cirrhosis) are shown in **Table 12**.

Table 12. Sustained Virologic Response (SVR12) in Treatment-Naive Patients and Patients Experienced[a] to Peginterferon, Ribavirin, and/or Sofosbuvir with or without Cirrhosis after 8 or 12 Weeks of Treatment with MAVIRET (pooled data from ENDURANCE-1, -2, -4, SURVEYOR-1, -2, and EXPEDITION-1, and -4)

	GT-1[b] % (n/N)	GT-2 % (n/N)	GT-4 % (n/N)	GT-5 % (n/N)	GT-6 % (n/N)
SVR12 in subjects without cirrhosis					
8 weeks	99.0 (383/387)	98.0 (193/197)	93.5 (43/46)	100 (2/2)	90.0 (9/10)
Outcome for subjects without SVR12					
On-treatment VF	0.3 (1/387)	0 (0/197)	0 (0/46)	0 (0/2)	0 (0/10)
Relapse[c]	0 (0/384)	1.0 (2/195)	0 (0/45)	0 (0/2)	0 (0/10)
Other[d]	0.8 (3/387)	1.0 (2/197)	6.5 (3/46)	0 (0/2)	10 (1/10)
SVR12 in subjects with cirrhosis					
12 weeks	97.0 (98/101)	100 (35/35)	100 (20/20)	100 (2/2)	100 (7/7)
Outcome for subjects without SVR12					
On-treatment VF	0 (0/101)	0 (0/35)	0 (0/20)	0 (0/2)	0 (0/7)
Relapse[c]	1.0 (1/98)	0 (0/35)	0 (0/19)	0 (0/2)	0 (0/7)
Other[d]	2.0 (2/101)	0 (0/35)	0 (0/20)	0 (0/2)	0 (0/7)

GT = genotype; VF = virologic failure

a. Percent of patients with prior treatment experience to PRS is 35%, 14%, 23%, 0%, and 18% for genotypes 1, 2, 4, 5, and 6, respectively. None of the GT-5 patients were TE-PRS, and 3 GT-6 patients were TE-PRS.

b. Includes 15 patients co-infected with HIV-1 (treated for 8 weeks).

c. Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

d. Includes patients who discontinued due to adverse event, lost to follow-up, or patient withdrawal.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups of patients treated with MAVIRET for the recommended duration as summarized in **Table 13.**

Table 13. Sustained Virologic Response (SVR12) in Selected Subgroups of Treatment-Naive Patients and Patients Experienced to Peginterferon, Ribavirin, and/or Sofosbuvir , Infected with HCV Genotypes 1, 2, 4, 5 or 6 without Cirrhosis Treated for 8 weeks and with Cirrhosis Treated for 12 weeks (Phase 2, 3 Studies[a])

SVR12	Genotype				Total
	GT-1 N=477 % (n/N)	GT-2 N=228 % (n/N)	GT-4 N=62 % (n/N)	GT-5, -6 N=21 % (n/N)	N=788 % (n/N)
HCV Genotype/ Subtype					
1a	97.8 (223/228)	NA	NA	NA	97.8 (223/228)
1b	100 (247/247)	NA	NA	NA	100 (247/247)
Prior Treatment History					
TN	99.0 (311/314)	99.0 (196/198)	94.1 (48/51)	94.4 (17/18)	98.5 (572/581)
Cirrhotic	100 (66/66)	100 (24/24)	100 (12/12)	100 (8/8)	100 (110/110)
Non-cirrhotic	98.8 (245/248)	98.9 (172/174)	92.3 (36/39)	90 (9/10)	98.1 (462/471)
TE-PRS	98.8 (161/163)	93.3 (28/30)	100 (11/11)	100 (3/3)	98.1 (203/207)
P/R-experienced	98.7 (156/158)	94.4 (17/18)	100 (10/10)	100 (3/3)	98.4 (186/189)
SOF-experienced	100 (5/5)	91.7 (11/12)	100 (1/1)	NA	94.4 (17/18)
HCV/HIV Coinfection[b]					
Yes	100 (15/15)	NA	NA	NA	100 (15/15)
No	98.9 (457/462)	98.2 (224/228)	95.2 (59/62)	95.2% (20/21)	98.3 (760/773)

GT = genotype; P/R = peginterferon/ribavirin; TN = treatment-naïve; TE = treatment-experienced; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SOF = sofosbuvir.
a. Population excludes patients with severe renal impairment (Study M15-462), including only patients administered the recommended duration of MAVIRET: 8 weeks for non-cirrhotics patients and 12 weeks for cirrhotic patients.
b. Baseline HIV antiretroviral combination regimens used: dolutegravir/abacavir/lamuvidine (n = 4), raltegravir plus emtricitabine/tenofovir disoproxil fumarate (n = 6), rilpivirine/emtricitabine/tenofovir disoproxil fumarate (n = 3), dolutegravir plus emtricitabine/tenofovir disoproxil fumarate (n = 1), raltegravir plus abacavir/lamuvidine (n = 1)

High SVR12 rates were achieved across all HCV genotypes in all subgroups including by age, gender, race, ethnicity, BMI, HCV RNA level, cirrhosis status, HIV coinfection, prior treatment history and IL28B genotype. The SVR12 rate of MAVIRET across all treatment-naïve patients without cirrhosis with genotype 1, 2, 4, 5, 6 chronic HCV infection treated for 8 weeks was 98.1% (462/471) with no virologic failures.

Clinical Studies in Genotype 3 Infected Patients

Demographic and Other Baseline Characteristics

The efficacy of MAVIRET in patients who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir with genotype 3 chronic hepatitis C infection was demonstrated in the ENDURANCE-3 (treatment-naïve without cirrhosis) and SURVEYOR-2 Parts 1-3 (patients with and without cirrhosis and treatment-naïve and/or treatment-experienced) clinical studies.

ENDURANCE-3 was a partially-randomized, open-label, active-controlled study in treatment-naïve patients. Patients were randomized (2:1) to either MAVIRET for 12 weeks or the combination of sofosbuvir and daclatasvir for 12 weeks; subsequently the study included a third arm (which was non-randomized) with MAVIRET for 8 weeks. SURVEYOR-2 Part 3 was an open-label study randomizing non-cirrhotic treatment-experienced patients to 12- or 16-weeks of treatment; in addition, the study evaluated the efficacy of MAVIRET in patients with compensated cirrhosis and genotype 3 infection in two dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (treatment-experienced only) durations. Among treatment-experienced patients, 46% (42/91) failed a previous regimen containing sofosbuvir.

The demographic and disease characteristics of the population with HCV genotype 3 infection in ENDURANCE-3 and SURVEYOR-2 are summarized in **Table 14**.

Table 14. Demographic and Other Baseline Characteristics of the Patient Population Infected with HCV Genotypes 3 (ENDURANCE-3, SURVEYOR-2)

Characteristics	MAVIRET 8, 12 or 16 Weeks N=632 n (%)
Age (years)	
< 65	596 (94.3)
≥65	36 (5.7)
Gender	
Male	367 (58.1)
Female	265 (41.9)
Race	
White	558 (88.3)
Black	9 (1.4)
Asian	47 (7.4)
Other	18 (2.8)
Viral Load	
HCV RNA (Log_{10} IU/mL) mean (SD)	6.2 (0.79)
BMI	
< 30 kg/m^2	509 (80.5)
≥ 30 kg/m^2	123 (19.5)
HCV Genotype/Subtype	
3a	587 (92.9)
3-other	45 (7.1)
Prior Treatment History	
TN	510 (80.7)
TE-PRS	122 (19.3)
P/R-experienced	80 (12.7)
SOF-experienced	42 (6.6)
Stages of Fibrosis	
F0-F2	440 (69.6)
F3	78 (12.3)
F4	114 (18.0)
Cirrhosis	
Yes	115 (18.2)
No	517 (81.8)

P/R = peginterferon/ribavirin; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SD = standard deviation; TE = treatment-experienced; TN = treatment-naïve

Study Results

The response rates of the treatment-naïve genotype 3-infected patients without cirrhosis treated with MAVIRET for 8 and 12 weeks and patients treated with sofosbuvir and daclatasvir for 12 weeks are presented in **Table 15**.

Table 15. Sustained Virologic Response (SVR12) in Treatment-Naïve Patients Infected with HCV Genotype 3 without Cirrhosis (ENDURANCE-3)

	MAVIRET 8 weeks N=157 % (n/N)	**MAVIRET 12 weeks N=233 % (n/N)**	**SOF+DCV 12 weeks N=115 % (n/N)**
SVR	94.9 (149/157)	95.3 (222/233)[a]	96.5 (111/115)[b]
Outcome for patients without SVR			
On-treatment VF	0.6 (1/157)	0.4 (1/233)	0 (0/115)
Relapse[c]	3.3 (5/150)	1.4 (3/222)	0.9 (1/114)
Other[d]	1.3 (2/157)	3.0(7/233)	2.6 (3/115)
Outcome by HCV genotype/subtype			
3a	94.9 (148/156)	95.7 (220/230)	96.5 (111/115)
3-other	100 (1/1)	66.7 (2/3)	NA

VF = virologic failure; SOF = sofosbuvir; DCV = daclatasvir; NA = not applicable.

a. Treatment difference between MAVIRET for 8 weeks and MAVIRET for 12 weeks was -0.4%; 97.5% confidence interval (-5.4% to 4.6%).

b. Treatment difference between MAVIRET for 12 weeks and SOF+DCV was -1.2%; 95% confidence interval (-5.6% to 3.1%).

c. Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

d. Includes patients who discontinued due to adverse event, lost to follow-up, or patient withdrawal.

The response rates in genotype 3-infected treatment-naive patients with cirrhosis treated with MAVIRET for 12 weeks and PRS treatment-experienced patients with or without cirrhosis treated with MAVIRET for 16 weeks in SURVEYOR-2 Part 3 are presented in **Table 16**.

Table 16. Sustained Virologic Response (SVR12) in Treatment-Naive Patients and Patients Experienced to Peginterferon, Ribavirin, and/or Sofosbuvir, Infected with HCV Genotype 3 with or without Cirrhosis (SURVEYOR-2 Part 3)

	Treatment-Naïve with Cirrhosis	Treatment-Experienced with or without Cirrhosis
	MAVIRET 12 weeks (N=40) % (n/N)	**MAVIRET 16 weeks (N=69) % (n/N)**
SVR	97.5 (39/40)	95.7 (66/69)
Outcome for patients without SVR		
On-treatment VF	0 (0/40)	1.4 (1/69)
Relapse[a]	0 (0/39)	2.9 (2/68)
Other[b]	2.5 (1/40)	0 (0/69)
Outcome in selected subgroups		
HCV Genotype/Subtype		
3a	97.4 (38/39)	95.5 (64/67)
3-other	100 (1/1)	100 (2/2)
Prior Treatment History		
TN	97.5 (39/40)	NA
TE-PRS	NA	95.7 (66/69)
P/R-experienced	NA	94.3 (33/35)
SOF-experienced	NA	97.1 (33/34)

VF = virologic failure; TN = treatment-naïve; TE = treatment-experienced; PRS = regimens containing interferon, pegylated interferon, ribavirin and/or sofosbuvir; P/R = peginterferon/ribavirin; SOF = sofosbuvir.

a. Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

b. Includes patients who discontinued due to adverse event, lost to follow-up, or patient withdrawal.

The SVR12 rate of MAVIRET across all treatment-naïve patients without cirrhosis with genotype 3 chronic HCV infection treated in Phase 2 and 3 studies (ENDURANCE-3 or SURVEYOR-2 Parts 1 and 2) was 95.2% (177/186) with 2.8% relapse (5/178) for patients treated for 8 weeks, and 95.4% (248/260) with 1.2% relapse (3/248) for patients treated for 12 weeks.

Of the genotype 3-infected patients with end stage renal disease enrolled in EXPEDITION-4, 100% (11/11) achieved SVR12.

Among treatment-experienced patients treated for 16 weeks, SVR12 rates were 95% (n=22) in patients without cirrhosis and 96% (n=47) in patients with cirrhosis.

High SVR12 rates were achieved across all subgroups including by age, gender, race, ethnicity, BMI, HCV RNA level, cirrhosis status, prior treatment history and IL28B genotype.

SVR12 rate in all GT-3 patients irrespective of cirrhosis status or prior treatment history treated with MAVIRET for the recommended durations was 95.7% (n=324) with 3.0% virologic failures.

Clinical Study in Chronic Kidney Disease (CKD) Patients

Demographic and Other Baseline Characteristics

The demographic and disease characteristics of the population with stages 4 and 5 chronic kidney disease are summarized in **Table 17**.

Table 17. Demographic and Other Baseline Characteristics of the Patient Population with and without Cirrhosis with Chronic Kidney Disease (Stages 4, 5) Infected with HCV Genotypes 1 to 6 (EXPEDITION-4)

Characteristics	MAVIRET 12 Weeks N=104 n (%)
Age	
< 65	76 (73.1)
≥ 65	28 (26.9)
Gender	
Male	79 (76.0)
Female	25 (24.0)
Race	
White	64 (61.5)
Black	25 (24.0)
Asian	9 (8.7)
Other	6 (5.8)
Viral Load	
HCV RNA (Log_{10} IU/mL), mean (SD)	5.85 (0.74)
BMI	
< 30 kg/m^2	79 (76.0)
≥ 30 kg/m^2	25 (24.0)
HCV Genotype/Subtype	
1a	23 (22.1)
1b	29 (27.9)
2	17 (16.3)
3	11 (10.6)
4	20 (19.2)
5 and 6	2 (2.0)
Prior Treatment History	
TN	60 (57.7)
TE-PRS	44 (42.3)
P/R-experienced	42 (40.4)
SOF-experienced	2 (1.9)
Stages of Fibrosis	
F0-F2	69 (66.3)
F3	17 (16.3)
F4	17 (16.3)

Cirrhosis	
Yes	20 (19.2)
Child Pugh Score 5 cirrhosis	15 (14.4)
Child Pugh Score 6 cirrhosis	4 (3.8)
Child Pugh Score > 6 cirrhosis[a]	1 (1.0)
No	84 (80.8)
Stages of Chronic Kidney Disease	
Stage 4 without dialysis[b]	13 (12.5)
Stage 5 without dialysis[c]	6 (5.8)
Stage 5 requiring dialysis[d]	85 (81.7)

P/R = peginterferon/ribavirin; BMI = body mass index; GT = genotype; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SD = standard deviation; TE = treatment-experienced; TN = treatment-naïve.

a. one patient had Child Pugh Score 7 at baseline.

b. Stage 4, defined as patients with eGFR 15 to 30 mL/min/1.73 m^2.

c. Stage 5 defined as eGFR < 15 mL/min/1.73 m^2

d. Stage 5, requiring routine dialysis. 19% (16/85) of the patients requiring dialysis had cirrhosis, mostly of Child-Pugh 5 and 6.

Study Results

The response rates in patients with CKD (stages 4 and 5) infected with HCV genotypes 1 to 6 are presented in **Table 18**.

Table 18. Sustained Virologic Response (SVR12) in Chronic Kidney Disease (Stages 4 and 5), HCV Genotypes 1to 6 Infected Patients with or without Cirrhosis (EXPEDITION-4)

Assessment	**MAVIRET 12 Weeks N=104 % (n/N)**
SVR12	98.1 (102/104)
95% CI	(95.4, 100)
Outcomes in Patients Without SVR	
On Treatment VF	0 (0/104)
Relapse[a]	0 (0/104)
Other[b]	1.9 (2/104)

VF = virologic failure; P/R = peginterferon/ribavirin; GT = genotype; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

a. Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

b. Includes patients who discontinued due to adverse event, lost to follow-up, or patient withdrawal.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups as summarized in **Table 19**.

Table 19. Sustained Virologic Response (SVR12) in Selected Subgroups of Chronic Kidney Disease (Stages 4 and 5 Patients Infected with HCV Genotypes 1 to 6 (EXPEDITION-4)

Subgroups	MAVIRET 12 Weeks N=104 % (n/N)
Genotypes	
1	96.4 (53/55)
2	100 (16/16)
3	100 (11/11)
4	100 (20/20)
5 and 6	100 (2/2)
Cirrhosis	
Yes	90 (18/ 20)
No	100 (84/84)
Child-Pugh Score	
5	86.7 (13/ 15)
6	100 (4/4)
≥ 6	100 (1/1)
Baseline CKD Stage	
Stage 4 without dialysis[a]	100 (13/13)
Stage 5 without dialysis[b]	100 (6/6)
Stage 5 requiring dialysis[c]	97.6 (83/85)
Prior Treatment History	
TN	96.7 (58/60)
TE-PRS	100 (44/44)
P/R-experienced	100 (42/42)
SOF-experienced	100 (2/2)

P/R = peginterferon/ribavirin; GT = genotype; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; TE = treatment-experienced; TN = treatment-naïve.

a. Stage 4, defined as patients with eGFR 15 to 30 mL/min/1.73 m^2.

b. Stage 5, defined as eGFR < 15 mL/min/1.73 $m^{2.}$

c. Stage 5, requiring routine dialysis.

Among patients with advanced renal disease, high SVR12 rates were achieved across all subgroups including by age, gender, race, ethnicity, BMI, HCV RNA level, cirrhosis status, prior treatment history, CKD stage and IL28B genotype.

Among all patients, regardless of renal function or cirrhosis status, who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin, and/or sofosbuvir and infected

with any HCV genotype who received the recommended treatment duration, 97.4% (1102/1131) achieved SVR12, 0.3% (3/1131) experienced on-treatment virologic failure, and 1.0% (11/1111) experienced post-treatment relapse. For the subset of patients with compensated cirrhosis, 97.5% (274/281) achieved SVR12.

Clinical Studies in NS5A Inhibitor and/or Protease Inhibitor (NS3/4A) Treatment-Experienced Patients with or without Cirrhosis

Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for NS5A inhibitor and/or NS3/4A protease inhibitor (PI) treatment-experienced patients with or without cirrhosis with genotype 1 HCV infection in MAGELLAN-1 Part 2 are provided in **Table 20**.

Table 20. Demographic and Other Baseline Characteristics of NS5A Inhibitor and/or NS3/4A Protease Inhibitor Treatment-Experienced Patients Infected with HCV Genotypes 1 (MAGELLAN-1 Part 2)

Characteristics	MAVIRET 12 Weeks N=43 % (n/N)	MAVIRET 16 Weeks N=44 % (n/N)
Age		
< 65	93.0 (40/43)	81.8 (36/44)
≥ 65	7.0 (3/43)	18.2 (8/44)
Gender		
Male	69.8 (30/43)	72.7 (32/44)
Female	30.2 (13/43)	27.3 (12/44)
Race		
White	79.1(34/43)	79.5 (35/44)
Black	18.6 (8/43)	18.2 (8/44)
Asian	2.3 (1/43)	2.3 (1/44)
BMI		
< 30 kg/m^2	67.4 (29/43)	56.8 (25/44)
≥ 30 kg/m^2	32.6 (14/43)	43.2 (19/44)
HCV Genotypes		
1	100 (43/43)	97.7 (43/44)
1a	81.4 (35/43)	72.7 (32/44)
1b	18.6 (8/43)	25.0 (11/44)
HCV RNA Viral Load (Log_{10} IU/mL), mean (SD)	6.02 (0.67)	6.24 (0.57)
Fibrosis Stage		
F0-F2	51.2 (22/43)	70.5 (31/44)
F3	16.3 (7/43)	6.8 (3/44)
F4	32.6 (14/43)	22.7 (10/44)
Cirrhosis		
Yes	34.9 (15/43)	22.7 (10/44)
No	65.1 (28/43)	77.3 (34/44)

Previous DAA Experience[a]		
PI experienced only	32.6 (14/43)	27.3 (12/44)
With Cirrhosis	16.3 (7/43)	9.1 (4/44)
Without Cirrhosis	16.3 (7/43)	18.2 (8/44)
NS5A experienced only	37.2 (16/43)	38.6 (17/44)
With Cirrhosis	16.3 (7/43)	6.8 (3/44)
Without Cirrhosis	20.9 (9/43)	31.8 (14/44)
NS5A and PI experienced	30.2 (13/43)	34.1 (15/44)
With Cirrhosis	2.3 (1/43)	6.8 (3/44)
Without Cirrhosis	27.9 (12/43)	27.3 (12/44)

NS5A = nonstructural viral protein 5A; PI = protease inhibitor

a. DAA experience was considered additive, i.e., a subject treated in the past with PI-containing regimen (e.g., TVR + PR) and subsequently with an NS5A-containing regimen (e.g., LDV + SOF) was considered NS5A- and PI-experienced.

Study Results

The response rates in patients with NS5A inhibitor and/or NS3/4A PI treatment experience with or without cirrhosis in MAGELLAN-1 Part 2 are presented in **Table 22**. The SVR12 rate in patients in MAGELLAN-1 Part 1 and Part 2 with prior PI or NS5A inhibitor treatment experience treated with MAVIRET for the recommended duration was 92.9% (n=42) with 2.4% virologic failure.

Table 21. Sustained Virologic Response (SVR12) in NS5A Inhibitor and/or NS3/4A Protease Inhibitor Treatment-Experienced Patients Infected with HCV Genotypes 1 with or without Cirrhosis (MAGELLAN-1 Part 2)

Assessment	MAVIRET 12 Weeks N=43 % (n/N)	MAVIRET 16 Weeks N=44 % (n/N)
SVR12	88.4 (38/43)	90.9 (40/44)
95% CI	(75.5, 94.9)	(78.8, 96.4)
Outcome in Patients Without SVR		
Virologic Failure	11.6 (5/43)	9.1 (4/44)
On treatment VF	2.3 (1/43)	9.1 (4/44)
Relapse[a]	9.5 (4/42)	0 (0/40)

VF = virologic failure

a. Relapse is defined as HCV RNA ≥ LLOQ after end-of-treatment response among those who completed treatment.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups as summarized in **Table 22**.

Table 22. Sustained Virologic Response (SVR12) in Selected Subgroups of NS5A Inhibitor and/or NS3/4A Protease Inhibitor Treatment-Experienced Patients Infected with HCV Genotypes 1 (MAGELLAN-1 Part-2)

Subgroups	MAVIRET 12 Weeks N=43 % (n/N)	MAVIRET 16 Weeks N=44 % (n/N)
Cirrhosis		
Yes	93.3 (14/15)	70.0 (7/10)
No	85.7 (24/28)	97.1 (33/34)
Previous DAA Regimen class		
PI only	100 (14/14)	100 (12/12)
NS5A Inhibitors only[a]	87.5 (14/16)	94.1 (16/17)
NS5A Inhibitors and PI	76.9 (10/13)	80 (12/15)
Presence of Key Baseline Substitutions[b]		
None	100 (13/13)	100 (13/13)
NS3 only	100 (2/2)	100 (4/4)
NS5A only	83.3 (20/24)	95.2 (20/21)
Both NS3 and NS5A[c]	75.0 (3/4)	25.0 (1/4)

NS5A = nonstructural viral protein 5A; PI = protease inhibitor

a. Includes patients who previously failed LDV or DCV containing regimens.

b. Detected by next generation sequencing using 15% detection threshold at amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A in patients who had baseline sequences available.

c. In a limited number of patients significantly lower SVR12 rates were observed at the studied treatment durations of 12 and 16 weeks

High SVR12 rates were achieved in patients who failed a prior treatment containing NS5A inhibitors (ledipasvir or daclatasvir) and in patients with pre-existing NS5A substitutions (while PI-naïve and without pre-existing treatment emergent NS3 substitutions in positions 155, 156 and 168) treated with MAVIRET for the recommended duration (16 weeks). High SVR12 rates were achieved in patients with prior failure to a protease inhibitor only (while NS5A-inhibitor naïve) treated for the recommended duration (12 weeks). Lower efficacy was observed in patients who previously failed both NS5A inhibitors and NS3/4A PIs and had pre-existing treatment emergent substitutions in both NS5A and NS3.

MICROBIOLOGY

Description

MAVIRET is a fixed-dose bilayer tablet (3X) combination regimen of glecaprevir and pibrentasvir.

Antiviral Activity *in vitro*

Glecaprevir

Glecaprevir is a pangenotypic inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, glecaprevir inhibited the proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a with IC50 value ranging from 3.5 to 11.3 nM.

Pibrentasvir

Pibrentasvir is a pangenotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of pibrentasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Combination Activity

Evaluation of combination of glecaprevir and pibrentasvir showed no antagonism in antiviral activity in HCV genotype 1 replicon cell culture assays.

Antiviral Activity in Cell Culture

The EC_{50} values of glecaprevir and pibrentasvir against full-length or chimeric replicons encoding NS3 or NS5A from laboratory strains are presented in **Table 23**.

Table 23. Activity of Glecaprevir and Pibrentasvir Against HCV Genotypes 1 to 6 Replicon Cell Lines

HCV Subtype	Glecaprevir EC_{50}, nM[a]	Pibrentasvir EC_{50}, nM[b]
1a	0.85	0.0018
1b	0.94	0.0043
2a	2.2	0.0023
2b	4.6	0.0019
3a	1.9	0.0021
4a	2.8	0.0019
5a	NA	0.0014
6a	0.86	0.0028

NA = not available

a. Stable replicon cell lines containing full-length NS3-5B from genotypes 1a, 1b, or 2a; or chimeric replicons containing NS3 from genotype 2b, 3a, 4a, or 6a.

b. Stable replicon cell lines containing full-length NS3-5B from genotype 1a or 1b; or chimeric replicons containing NS5A from genotype 2a, 2b, 3a, 4a, 5a, or 6a.

The EC_{50} values of glecaprevir and pibrentasvir against chimeric replicons encoding NS3 or NS5A from clinical isolates are presented in **Table 24**.

Table 24. Activity of Glecaprevir and Pibrentasvir against Transient Replicons Containing NS3 or NS5A from HCV Genotypes 1 to 6 Clinical Isolates

HCV Subtype	Glecaprevir		Pibrentasvir	
	Number of clinical isolates	Median EC_{50}, nM (range)	Number of clinical isolates	Median EC_{50}, nM (range)
1a	11	0.08 (0.05 – 0.12)	11	0.0009 (0.0006 – 0.0017)
1b	9	0.29 (0.20 – 0.68)	8	0.0027 (0.0014 – 0.0035)
2a	4	1.6 (0.66 – 1.9)	6	0.0009 (0.0005 – 0.0019)
2b	4	2.2 (1.4 – 3.2)	11	0.0013 (0.0011 – 0.0019)
3a	2	2.3 (0.71 – 3.8)	14	0.0007 (0.0005 – 0.0017)
4a	6	0.41 (0.31 – 0.55)	8	0.0005 (0.0003 – 0.0013)
4b	NA	NA	3	0.0012 (0.0005 – 0.0018)
4d	3	0.17 (0.13 – 0.25)	7	0.0014 (0.0010 – 0.0018)
5a	1	0.12	1	0.0011
6a	NA	NA	3	0.0007 (0.0006 – 0.0010)
6e	NA	NA	1	0.0008
6p	NA	NA	1	0.0005

NA = not available

Resistance

In Cell Culture

Amino acid substitutions in NS3 or NS5A selected in cell culture or important for the inhibitor class were phenotypically characterized in replicons.

Substitutions important for the HCV protease inhibitor class at positions 36, 43, 54, 55, 56, 155, 166, or 170 in NS3 had no impact on glecaprevir activity. Individual substitutions at NS3 amino acid position A156 introduced into HCV replicons by site-directed mutagenesis generally caused the greatest reductions (>100-fold) in susceptibility to glecaprevir. Individual substitutions at NS3 position D/Q168 had varying effects on glecaprevir susceptibility depending on HCV genotype/subtype and specific amino acid change, with the greatest reductions (>30-fold) observed in genotypes 1a (D168F/Y), 3a (Q168R) and 6a (D168A/G/H/V/Y). Combinations of NS3 Y56H plus D/Q168 substitutions resulted in greater reductions in glecaprevir susceptibility. An NS3 Q80R substitution in genotype 3a caused a 21-fold reduction in glecaprevir susceptibility, while Q80 substitutions in genotypes 1a and 1b (including genotype 1a Q80K) did not reduce glecaprevir susceptibility.

Single substitutions important for the NS5A inhibitor class at positions 24, 28, 30, 31, 58, 92, or 93 in NS5A in genotypes 1 to 6 had no impact on the activity of pibrentasvir. Amino acid substitutions resulting from multiple nucleotide changes reduced susceptibility to pibrentasvir in a genotype 1a replicon (M28G or Q30D, 244- and 94-fold, respectively), and in a genotype 1b replicon (P32-deletion, 1,036-fold). Some combinations of two or more NS5A inhibitor resistance-associated amino acid substitutions may result in greater reductions in pibrentasvir susceptibility. Specifically in genotype 3a, A30K or Y93H had no impact on pibrentasvir activity. Some combinations of substitutions in genotypes 1a and 3a (including A30K+Y93H in genotype 3a) showed reductions in susceptibility to pibrentasvir.

In Clinical Studies

Studies in Treatment-Naïve and Peginterferon, Ribavirin and/or Sofosbuvir Treatment-Experienced Patients with or without Cirrhosis

Twenty two of the approximately 2,300 patients treated with MAVIRET for 8, 12, or 16 weeks in Phase 2 and 3 clinical studies experienced virologic failure (2 with genotype 1, 2 with genotype 2, 18 with genotype 3 infection). In addition, 1 GT-3-infected patient experiencing virologic failure was determined to be reinfected with a GT-3 virus distinct from the one present at baseline. Among the 22 patients experiencing virologic failure, treatment-emergent substitutions were detected in 54.5% (12/22) of patients in NS3 and 81.8% (18/22) of patients in NS5A.

Among the 2 genotype 1-infected patients who experienced virologic failure, one had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.

Among the 2 genotype 2-infected patients, no treatment-emergent substitutions were observed in NS3 or NS5A (the M31 polymorphism in NS5A was present at baseline and post-treatment in both patients).

Among the 18 genotype 3-infected patients treated with MAVIRET for 8, 12, or 16 weeks who experienced virologic failure, treatment-emergent NS3 substitutions Y56H/N, Q80K/R, A156G, or Q168L/R were observed in 11 patients. A166S or Q168R were present at baseline and post-treatment in 5 patients. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in 16 patients, and 13 patients had A30K (n=9) or Y93H (n=5) at baseline and post-treatment.

Studies in Patients with or without Cirrhosis Who Were Treatment-Experienced to NS3/4A Protease and/or NS5A Inhibitors

Ten of 113 patients treated with MAVIRET in the MAGELLAN-1 study for 12 or 16 weeks experienced virologic failure.

Among the 10 genotype 1-infected patients with virologic failure, treatment-emergent NS3 substitutions V36A/M, R155K/T, A156G/T/V, or D168A/T were observed in 7 patients. Five of the 10 had combinations of V36M, Y56H, R155K/T, or D168A/E in NS3 at baseline and post-treatment. All of the genotype 1-infected virologic failure patients had one or more NS5A substitutions L/M28M/T/V, Q30E/G/H/K/L/R, L31M, P32deletion, H58C/D, or Y93H at baseline, with additional treatment-emergent NS5A substitutions M28A/G, P29Q/R, Q30K, H58D, or Y93H observed in 7 of the patients at the time of failure.

Effect of Baseline HCV Substitutions/Polymorphisms on Treatment Response

A pooled analysis of treatment-naïve and pegylated interferon, ribavirin and/or sofosbuvir treatment-experienced patients receiving MAVIRET in the Phase 2 and Phase 3 clinical studies was conducted to explore the association between baseline polymorphisms and treatment outcome and to describe substitutions seen upon virologic failure. Baseline polymorphisms relative to a subtype-specific reference sequence at amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A were evaluated at a 15% detection threshold by next-generation sequencing. Baseline polymorphisms in NS3 at any of the above-listed amino acid positions were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of patients with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively. Baseline polymorphisms in NS5A at any of the above-listed amino acid positions were detected in 26.8% (225/841), 79.8% (331/415), 22.1% (136/615), 49.7% (80/161), 12.9 % (4/31), and 54.1% (20/37) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively. The prevalence of baseline polymorphisms in NS3 was higher in GT-5 as compared to other genotypes; the high prevalence in GT-5 was due to the common D168E polymorphism, which remains susceptible to glecaprevir. In general, with the exception of GT-5, the prevalence of baseline polymorphisms was higher in NS5A than in NS3.

Genotype 1, 2, 4, 5, and 6: The presence of baseline polymorphism in NS3 and NS5A did not have an impact on SVR12 rates for GT-1, -2, -4, -5 and -6.

Genotype 3: Among 309 genotype 3-infected patients receiving the recommended duration, baseline NS3 polymorphisms had no impact on treatment outcome. All patients 100% (15/15) with Y93H in NS5A at baseline achieved SVR12. Among patients receiving the recommended duration, 75% (15/20) with A30K in NS5A at baseline achieved SVR12. Among genotype 3-infected patients without cirrhosis receiving the recommended regimen, 91.4% (53/58) who had polymorphisms in NS5A at baseline achieved SVR12. Among genotype 3-infected patients with compensated cirrhosis receiving the recommended regimen, 100% (18/18) who had polymorphisms in NS5A at baseline achieved SVR12.

Cross-resistance

In vitro

In vitro data indicate that the majority of the resistance-associated substitutions in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, or 93 that confer resistance to ombitasvir, daclatasvir,

ledipasvir, elbasvir, or velpatasvir remained susceptible to pibrentasvir. Glecaprevir was fully active against resistance-associated substitutions in NS5A, while pibrentasvir was fully active against resistance-associated substitutions in NS3. Both glecaprevir and pibrentasvir were fully active against substitutions associated with resistance to NS5B nucleotide and non-nucleotide inhibitors.

Clinical Studies

In the MAGELLAN-1 study, patients who had failed prior treatment with NS3/4A protease and/or NS5A inhibitors were treated with MAVIRET for 12 or 16 weeks. Baseline sequences were analyzed by next generation sequencing at 15% detection threshold. One or more of the following NS3 polymorphisms were detected at baseline in 16% (17/105) of patients with genotype 1 infection: R155K/T (n=8) or D168A/E/N/T/V (n=10). One or more of the following NS5A substitutions were detected in 60% (63/105) of the genotype 1-infected patients: K24Q/R (n=4), L/M28A/M/T/V (n=11), Q/R30E/G/H/K/L/Q/R (n=29), L31I/M/V (n=14), H/P58C/D/P/Q/S/T/Y (n=17), A92E/T (n=2), or Y93H/N/S (n=23). The number of GT-4-infected patients enrolled in the study was small, and did not allow for analysis of resistance.

Among 23 PI-experienced/NS5A inhibitor-naïve patients receiving 12 weeks of treatment, 2 patients each had baseline polymorphisms in NS3-only, NS5A-only, or NS3+NS5A; all 23 patients achieved SVR12. Among 32 NS5A inhibitor-experienced patients (with or without PI-experience) receiving 16 weeks of treatment, SVR12 rate was 100% (1/1), 95.0% (19/20), 25.0% (1/4), and 100% (7/7) in patients with baseline polymorphisms in NS3-only, NS5A-only, NS3+NS5A, or without any polymorphisms in NS3 or NS5A, respectively.

NON-CLINICAL TOXICOLOGY

Repeat-Dose Toxicity

Glecaprevir

Glecaprevir was well tolerated without adverse effects in studies for up to 1-month (mouse), 6-months (rat) and 9-months (dog). Maximum achieved glecaprevir plasma exposures in the longest duration studies were approximately 70 times (mice and rats) and 137 times (dog) higher when compared to human exposure at the recommended dose.

Pibrentasvir

Pibrentasvir was well tolerated without adverse effects in studies for up to 6-months (rat), 3-months (mouse) and 9-months (dog). Maximum achieved pibrentasvir plasma exposures in the longest duration studies were approximately 85 times (mice), 6 times (rat) and 17 times (dog) higher when compared to human exposure at the recommended dose.

Mutagenicity and Carcinogenicity

Glecaprevir and pibrentasvir were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo rodent micronucleus assays.

Carcinogenicity studies with glecaprevir and pibrentasvir have not been conducted.

Fertility

No effects on mating, female or male fertility, or early embryonic development were observed in rodents at up to the highest dose tested. Systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 63 and 102 times higher, respectively, the exposure in humans at the recommended dose.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

MAVIRET

glecaprevir/pibrentasvir tablets

Read this carefully before you start taking MAVIRET and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MAVIRET.

Serious Warnings and Precautions

Hepatitis B activity (e.g., inflamed liver) may increase when taking antiviral drugs like MAVIRET, sometimes leading to liver failure and death. (See the "**To help avoid side effects…**" section, *Hepatitis B Reactivation.*)

What is MAVIRET used for?

- MAVIRET treats people with chronic (long-lasting) hepatitis C in adults. Hepatitis C is caused by an infection with the hepatitis C virus (HCV).
- There are 2 medicines in MAVIRET. They are called glecaprevir and pibrentasvir.
- It is not known if taking MAVIRET is safe and effective in children under 18 years of age.

How does MAVIRET work?

MAVIRET works by stopping the hepatitis C virus from multiplying. This will help remove the virus from your blood over time.

What are the ingredients in MAVIRET?

Each tablet contains the following medicinal ingredients: glecaprevir, pibrentasvir.

Each tablet has the following ingredients that are not medicines: copovidone (type K 28), vitamin E polyethylene glycol succinate, colloidal silicon dioxide, propylene glycol monocaprylate (type II), croscarmellose sodium, sodium stearyl fumarate, hypromellose 2910, lactose monohydrate, titanium dioxide, polyethylene glycol 3350 and iron oxide red.

What does MAVIRET look like?

MAVIRET tablets are pink, oblong, film-coated tablets that are curved on both sides, and debossed on one side with 'NXT'.

MAVIRET comes in the following dosage forms:

Each tablet has 100 mg of glecaprevir and 40 mg of pibrentasvir.

Do not use MAVIRET if:

- you are allergic to any of the ingredients in MAVIRET. (See the section "**What are the ingredients in MAVIRET?**" to see all the ingredients.)
- your doctor has told you that you have severe loss of liver function.
- you are taking any of the following medicines:
    - atazanavir (Evotaz®, Reyataz®)
    - atorvastatin (Lipitor®)
    - dabigatran etexilate (Pradaxa®)
    - ethinyl estradiol-containing medicines such as tablets or vaginal rings used to prevent pregnancy
    - rifampin (Rifadin®, Rofact®)
    - simvastatin (Zocor®)

To help avoid side effects and make sure you are using your medicines correctly, talk to your doctor before you take MAVIRET. Talk about any health problems you may have, including if you:

- have liver problems other than hepatitis C infection.
- are taking other drugs for viral infections.
- are pregnant or plan to become pregnant. The effects of MAVIRET during pregnancy are not known. Avoid pregnancy while taking MAVIRET. Tell your doctor if you become pregnant while taking MAVIRET.
- are breastfeeding or plan to breastfeed. It is not known if MAVIRET passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take MAVIRET.
- have galactose intolerance (e.g., lactase deficiency or glucose-galactose malabsorption) as this product contains lactose.

Hepatitis B Reactivation

Taking antiviral drugs such as MAVIRET may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Talk to your doctor if:

- you have never been tested for hepatitis B.
- you know you have a current hepatitis B infection.
- you have had a previous hepatitis B infection.

Your doctor may order blood tests to see if you need hepatitis B treatment.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking MAVIRET.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

If you are taking any of the medicines in the table below, your doctor may need to change your dose of these medicines.

Medicines you must tell your doctor about before taking MAVIRET

Medicine	Purpose of the medicine
lovastatin pravastatin (Pravachol®) rosuvastatin (Crestor®)	to lower blood cholesterol
carbamazepine (Tegretol®) phenobarbital phenytoin (Dilantin®)	normally used for seizures
cyclosporine (Neoral®, Sandimmune®) tacrolimus (Prograf®)	to suppress the immune system
darunavir (Prezista®) efavirenz (Sustiva®, Atripla®) lopinavir/ritonavir (Kaletra®) rilpivirine (Edurant®, Complera®) ritonavir (Norvir®)	for HIV infection
digoxin (Lanoxin®)	for heart problems or high blood pressure
St John's Wort (*Hypericum perforatum*)	for mild depression
vitamin K antagonists (e.g., warfarin [Coumadin®])	to help reduce clots from forming in the blood

How to take MAVIRET:

- Take MAVIRET exactly as your doctor tells you. Do not change your dose or stop unless your doctor tells you to. If you reduce or miss a dose, the medicines may not be as effective against the virus.
- It is important that you do not miss or skip doses of MAVIRET during treatment.
- Swallow MAVIRET tablets whole. Do not chew, break, or crush MAVIRET tablets.

Usual adult dose:

- Take 3 MAVIRET tablets all at once each day with food. The type of food is not important.
- MAVIRET is taken for either 8, 12 or 16 weeks. Your doctor will tell you exactly how long you need to take MAVIRET.

Overdose:

If you think you have taken too much MAVIRET, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you do miss a dose and it is:

- less than 18 hours from the time you usually take MAVIRET - take the missed dose with food as soon as possible. Then take your next dose at your usual time.
- more than 18 hours from the time you usually take MAVIRET - do not take the missed dose. Take your next dose as usual with food.

Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using MAVIRET?

These are not all the possible side effects you may feel when taking MAVIRET. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of MAVIRET are tiredness and headache. You could also have nausea (feeling sick in the stomach).

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 2 and 30°C.
- Keep MAVIRET out of the reach and sight of children and adolescents under 18 years of age.

If you want more information about MAVIRET:

- Talk to your doctor.
- Find the most recent version of the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.canada.ca/en/health-canada), the manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

Last Revised: August 16, 2017

THE ATTACHED IS EXHIBIT "K" TO THE

AFFIDAVIT OF HEATHER RUMBLE PETERSON

SWORN BEFORE ME THIS 13TH DAY OF

OCTOBER, 2017

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
Province of Ontario, for Strosberg Sasso Sutts LLP,
Barristers and Solicitors.
Expires February 18, 2019.

Summary Safety Review - GALEXOS (simeprevir) - Assessing the Potential Risk of Severe Liver Problems

January 27, 2016

Product

Galexos (simeprevir)

Potential Safety Issue

Severe liver problems

Key Messages

- **Galexos (simeprevir) is a drug used to treat chronic hepatitis C.**
- **A safety review was carried out by Health Canada after Japan published a risk communication on severe liver problems and related death with simeprevir use.**
- **The prescribing information for Galexos has been updated with warnings about the risk of severe liver problems and related death. It also reminds healthcare professionals to frequently monitor patients for liver problems when using this drug.**

Overview

Health Canada carried out a safety review after Japan published a risk communication on severe liver problems and related death with the use of simeprevir. In patients with liver damage due to advanced chronic hepatitis C, increased levels of bilirubin in the blood can be a sign that the liver is not functioning properly. The use of simeprevir can further increase bilirubin levels in the blood; this risk is already included in the prescribing information.

Use in Canada

- Simeprevir has been marketed in Canada under the brand name of Galexos since 2013.

- Simeprevir is a drug used for the treatment of chronic hepatitis C. It is taken as an oral tablet for 12 weeks in combination with other medicinal products such as peginterferon alfa and ribavirin or with sofosbuvir.
- Recently, the number of prescriptions in Canada for simeprevir has gone from 1700 prescriptions between July and September 2014, to 16 prescriptions between July and September 2015.

Safety Review Findings

- At the time of the review, Health Canada had received 11 Canadian reports of severe liver problems, including 2 deaths, suspected of being linked with simeprevir. Upon review of these cases, no conclusions could be made regarding what role, if any, the drug may have played, due to limited information from these cases.
- In Japan, 8 cases of severe blood bilirubin levels and 3 deaths had been reported in association with simeprevir. Ethnic differences in susceptibility to liver problems exist, therefore the information from these cases needs to be interpreted with caution when considering the risk of simeprevir for other populations.
- Information was also received from the manufacturer about cases of severely abnormal bilirubin levels suspected of being linked with simeprevir. In some of these cases, the contribution of simeprivir to the side effect could not be ruled out.

Conclusions and Actions

- Based on all the information reviewed, Health Canada concluded that the prescribing information should be updated to reflect the level of evidence related to the risk of severe liver problems.
- The manufacturer of Galexos (simeprevir) has updated the prescribing information to:
    - Warn about the risk of severe liver problems and related death,
    - Advise healthcare professionals to do blood tests to check for liver function before and during treatment, and
    - Not use Galexos (simeprevir) in patients who have moderate or severe liver damage.
- Health Canada will publish a labelling update notice in the January 2016 issue of the Health Product InfoWatch to raise awareness of the labelling update for simeprevir.
- Health Canada will continue to monitor side effect information involving simeprevir, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action if and when any new health risks are identified.

Additional Information

The analysis that contributed to this safety review included scientific and medical literature, Canadian and international adverse reaction reports and what is known about the use of this drug both in Canada and internationally.

For additional information, contact the Marketed Health Products Directorate.

Date modified:

2016-02-03