רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

Exviera 250 mg Tablets

אקסווירה 250 מ"ג טבליות

Film coated tablets

Dasabuvir (as Sodium Monohydrate) 250 mg

חברת AbbVie Biopharmaceuticals Ltd. מבקשת להודיע כי העלונים לרופא ולצרכן של התכשיר עודכנו. בהודעה זו מצוינים סעיפים בהם נעשה שינוי מהותי או שינוי המהווה החמרה (שינוי שהינו הוספה מסומן בקו תחתון, מחיקה מסומנת בקו אמצעי). עדכונים נוספים אשר אינם מהווים החמרה או שאינם מהותיים, אינם נכללים בהודעה זו.

ההתוויה המאושרת לתכשיר:

Exviera is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

העלון לצרכן עודכן בסעיף הבא:

4. תופעות לוואי

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יש להפסיק את השימוש באקסווירה ולפנות מיד לרופא או לעזרה רפואית אם מתקיים אחד מהדברים הבאים:

תופעות לוואי בעת נטילה משולבת של אקסווירה ו-ombitasvir/paritaprevir/ritonavir עם או בלי ribavirin:

תופעות לוואי ששכיחותן אינה ידועה (לא ניתן להעריך על פי המידע הקיים):

- תגובות אלרגיות חמורות, סימנים עלולים לכלול:
  - קשיי נשימה או בליעה
  - סחרחורת, שעלולה להיגרם בעקבות לחץ דם נמוך
  - נפיחות של הפנים, שפתיים, לשון או גרון
  - פריחה או גירוד של העור

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העלון לרופא עודכן בסעיף הבא:

- **4.8 Undesirable effects**

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Post Marketing Adverse Reactions

~~*Hepatobiliary Disorders:* Hepatic decompensation, hepatic failure~~. The following post marketing adverse reactions have been observed during treatment with Exviera with ombitasvir/paritaprevir/ritonavir, with or without ribavirin ~~(see section 4.4).~~ The frequency of these events is unknown. The adverse reactions are presented by the System Organ Class.

Immune system disorders: Anaphylactic reactions.

Hepatobiliary disorders: Hepatic decompensation and hepatic failure (see section 4.4).

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העלונים המעודכנים לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, AbbVie Biopharmaceuticals Ltd, רחוב החרש 4, הוד השרון או בטלפון 7909600 – 09.

בברכה,
חופית שוורץ - רוקחת ממונה

This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved on June 2017, and it was updated according to the guidelines of the Ministry of Health on April 2018

1. NAME OF THE MEDICINAL PRODUCT

Exviera 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of dasabuvir (as sodium monohydrate).

Excipient with known effect: each film-coated tablet contains 44.94 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Beige, ovaloid, film-coated tablets with dimensions of 14.0 mm x 8.0 mm and debossed on one side with 'AV2'.

4. CLINICAL PARTICULARS

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with Exviera. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated

4.1 Therapeutic indications

Exviera is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.

4.2 Posology and method of administration

Treatment with Exviera should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

Posology

The recommended dose of dasabuvir is 250 mg (one tablet) twice daily (morning and evening).

Exviera must not be administered as monotherapy. Exviera should be used in combination with other medicinal products for the treatment of HCV (see section 5.1). Refer to the prescribing information of the medicinal products that are used in combination with Exviera.

The recommended co-administered medicinal product(s) and treatment duration for Exviera combination therapy are provided in table 1.

Table 1. Recommended co-administered medicinal product(s) and treatment duration for Exviera by patient population

Patient population	Treatment*	Duration
Genotype 1b, without cirrhosis or with compensated cirrhosis	Exviera + ombitasvir/paritaprevir/ritonavir	12 weeks 8 weeks may be considered in previously untreated genotype 1b-infected patients with minimal to moderate fibrosis** (see section 5.1, GARNET study)
Genotype 1a, without cirrhosis	Exviera + ombitasvir/paritaprevir/ritonavir + ribavirin*	12 weeks
Genotype 1a, with compensated cirrhosis	Exviera + ombitasvir/paritaprevir/ritonavir + ribavirin*	24 weeks (see section 5.1.)
*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection. ** When assessing severity of liver disease using non-invasive methods, a combination of blood biomarkers or the combination of liver stiffness measurement and a blood test improves accuracy and should be undertaken prior to 8 week treatment in all patients with moderate fibrosis.		

Missed doses
In case a dose of Exviera is missed, the prescribed dose can be taken within 6 hours. If more than 6 hours have passed since Exviera is usually taken, the missed dose should NOT be taken and the patient should take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

Special populations

HIV-1 Co-infection

Follow the dosing recommendations in Table 1. For dosing recommendations with HIV antiviral agents, refer to sections 4.4 and 4.5. See sections 4.8 and 5.1 for additional information.

Liver transplant recipients

Exviera and ombitasvir/paritaprevir/ritonavir 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 subjects received 600 to 800 mg per day (see section 5.1). For dosing recommendations with calcineurin inhibitors refer to section 4.5.

Elderly

No dose adjustment of Exviera is warranted in elderly patients (see section 5.2).

Renal impairment

No dose adjustment of Exviera is required for patients with mild, moderate, or severe renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment of Exviera is required in patients with mild hepatic impairment (Child-Pugh A).
Exviera is not recommended in patients with moderate hepatic impairment (Child-Pugh B) (see sections 4.4 and 4.8).
Exviera should not be used in patients with severe hepatic impairment (Child-Pugh C) (see section 5.2).

Paediatric population

The safety and efficacy of dasabuvir in children less than 18 years of age have not been established. No data are available.

Method of administration

The film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole (i.e. patients should not chew, break or dissolve the tablet). To maximise absorption, Exviera tablets should be taken with food, without regard to fat and calorie content (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Use of ethinylestradiol-containing medicinal products such as those contained in most combined oral contraceptives or contraceptive vaginal rings (see section 4.4 and 4.5).

Co-administration of Exviera with medicinal products that are strong or moderate enzyme inducers is expected to decrease dasabuvir plasma concentrations and reduce its therapeutic effect (see section 4.5). Examples of contraindicated inducers are provided below.

Enzyme inducers:

- carbamazepine, phenytoin, phenobarbital
- efavirenz, nevirapine, etravirine
- enzalutamide
- mitotane
- rifampicin
- St. John's Wort (*Hypericum perforatum*)

Medicinal products that are strong CYP2C8 inhibitors may increase dasabuvir plasma concentrations and must not be co-administered with Exviera (see section 4.5). Examples of contraindicated CYP2C8 inhibitors are provided below.

CYP2C8 inhibitor:

- gemfibrozil

Exviera is administered with ombitasvir/ paritaprevir /ritonavir. For contra-indications with ombitasvir/ paritaprevir /ritonavir refer to the prescribing information.

4.4 Special warnings and precautions for use

General

Exviera is not recommended for administration as monotherapy and must be used in combination with other medicinal products for the treatment of hepatitis C infection (see section 4.2 and 5.1).

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 postmarketing in patients treated with Exviera with ombitasvir/paritaprevir/ritonavir with and without ribavirin. Most patients with these severe outcomes had evidence of advanced or decompensated cirrhosis prior to initiating therapy. Although causality is difficult to establish due to background advanced liver disease, a potential risk cannot be excluded.

Exviera is not recommended in patients with moderate hepatic impairment (Child-Pugh B). Exviera should not be used in patients with severe hepatic impairment (Child-Pugh C) (see sections 4.2, 4.8 and 5.2).

For patients with cirrhosis:

- Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal haemorrhage).
- 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 dasabuvir and ombitasvir/paritaprevir/ritonavir with or without ribavirin, transient elevations of ALT to greater than 5 times the upper limit of normal occurred in approximately 1% of subjects (35 of 3,039). ALT elevations were asymptomatic and generally occurred during the first 4 weeks of treatment, without concomitant elevations of bilirubin, and declined within approximately two weeks of onset with continued dosing of dasabuvir and ombitasvir/paritaprevir/ritonavir with or without ribavirin.

These ALT elevations were significantly more frequent in the subgroup of subjects who were using ethinylestradiol -containing medicinal products such as combined oral contraceptives or contraceptive vaginal rings (6 of 25 subjects); (see section 4.3). In contrast, the rate of ALT elevations in subjects using other types of estrogens as typically used in hormonal replacement therapy (i.e., oral and topical estradiol and conjugated estrogens) was similar to the rate observed in subjects who were not using estrogen-containing products (approximately 1% in each group).

Patients who are taking ethinylestradiol -containing medicinal products (i.e. most combined oral contraceptives or contraceptive vaginal rings) must switch to an alternative method of contraception (e.g., progestin only contraception or non-hormonal methods) prior to initiating Exviera with ombitasvir/paritaprevir/ritonavir therapy (see sections 4.3 and 4.5).

Although ALT elevations associated with dasabuvir and ombitasvir/paritaprevir/ritonavir have been asymptomatic, patients should be instructed to watch for early warning signs of liver inflammation, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice and discoloured faeces, and to consult a doctor without delay if such symptoms occur. Routine monitoring of liver enzymes is not necessary in patients that do not have cirrhosis (for cirrhotics, see above). Early discontinuation may result in drug resistance, but implications for future therapy are not known.

Pregnancy and concomitant use with ribavirin

Also see section 4.6.

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients when Exviera is taken in combination with ribavirin, see section 4.6 and refer to the prescribing information for ribavirin for additional information.

Use with tacrolimus, sirolimus and everolimus

Co-administration of Exviera and ombitasvir/paritaprevir/ritonavir with systemic tacrolimus, sirolimus or everolimus increases the concentrations of the immunosuppressant due to CYP3A inhibition by ritonavir (see section 4.5). Serious and/or life threatening events have been observed with co-administration of Exviera and ombitasvir/paritaprevir/ritonavir with systemic tacrolimus, and a similar risk can be expected with sirolimus and everolimus.

Avoid concomitant use of tacrolimus or sirolimus with Exviera and ombitasvir/paritaprevir/ritonavir unless the benefits outweigh the risks. If tacrolimus or sirolimus are used together with Exviera and ombitasvir/paritaprevir/ritonavir, caution is advised, and recommended doses and monitoring strategies can be found in section 4.5. Everolimus cannot be used due to lack of suitable dose strengths for dose adjustments.

Tacrolimus or sirolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with Exviera and ombitasvir/paritaprevir/ritonavir 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 or sirolimus associated adverse events. Refer to the tacrolimus or sirolimus prescribing Information for additional dosing and monitoring instructions.

Depression or psychiatric illness

Cases of depression and more rarely of suicidal ideation and suicide attempt have been reported with Exviera with or without ombitasvir/paritaprevir/ritonavir treatment in combination with ribavirin in the majority of the cases. Although some cases had previous history of depression, psychiatric illness and/or substance abuse, a causal relation with Exviera with or without ombitasvir/paritaprevir/ritonavir treatment cannot be excluded. Caution should be used in patients with a pre-existing history of depression or psychiatric illness. Patients and caregivers should be instructed to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation.

Genotype-specific activity

Concerning recommended regimens with different HCV genotypes, see section 4.2. Concerning genotype-specific virological and clinical activity, see section 5.1.

The efficacy of dasabuvir has not been established in patients with HCV genotypes other than genotype 1; Exviera should not be used for the treatment of patients infected with other genotypes than 1.

Co-administration with other direct-acting antivirals against HCV

Exviera safety and efficacy have been established in combination with ombitasvir/ paritaprevir /ritonavir with or without ribavirin. Co-administration of Exviera with other antivirals has not been studied and, therefore, cannot be recommended.

Retreatment

The efficacy of dasabuvir in patients previously exposed to dasabuvir, or to medicinal products anticipated to be cross-resistant, has not been demonstrated.

Use with statins

Rosuvastatin
Dasabuvir with ombitasvir/paritaprevir/ritonavir is expected to increase the exposure to rosuvastatin more than 3-fold. If rosuvastatin treatment is required during the treatment period, the maximum daily dose of rosuvastatin should be 5 mg (see section 4.5, Table 2).

Pitavastatin and fluvastatin
The interactions with pitavastatin and fluvastatin have not been investigated. Theoretically, dasabuvir with ombitasvir/paritaprevir/ritonavir is expected to increase the exposure to pitavastatin and fluvastatin. A temporary suspension of pitavastatin/fluvastatin is recommended for the duration of treatment with ombitasvir/paritaprevir/ritonavir. If statin treatment is required during the treatment period, a switch to a reduced dose of pravastatin/rosuvastatin is possible (see section 4.5, Table 2).

Treatment of patients with HIV co-infection

Exviera is recommended in combination with paritaprevir/ombitasvir/ritonavir, and ritonavir may select for PI resistance in HIV co-infected patients without ongoing antiretroviral therapy. HIV co-infected patients without suppressive antiretroviral therapy should not be treated with dasabuvir.
Drug interactions need to be carefully taken into account in the setting of HIV co-infection (for details see section 4.5, Table 2).

Atazanavir can be used in combination with dasabuvir with ombitasvir/paritaprevir/ritonavir if administered at the same time. To be noted, atazanavir should be taken without ritonavir, since ritonavir 100 mg once daily is provided as part of the ombitasvir/paritaprevir/ritonavir fixed dose combination. The combination carries an increased risk for hyperbilirubinemia (including ocular icterus), in particular when ribavirin is part of the hepatitis C regimen.

Darunavir, dosed 800 mg once daily, if administered at the same time as ombitasvir/paritaprevir/ritonavir, can be used in the absence of extensive PI resistance (darunavir exposure lowered). To be noted, darunavir should be taken without ritonavir, since ritonavir 100 mg once daily is provided as part of the ombitasvir/paritaprevir/ritonavir fixed dose combination.

For the use of HIV protease inhibitors other than atazanavir and darunavir refer to the prescribing information of ombitasvir/ paritaprevir /ritonavir.

Raltegravir exposure is substantially increased (2-fold). The combination was not linked to any particular safety issues in a limited set of patients treated for 12-24 weeks.

Rilpivirine exposure is substantially increased (3-fold) when rilpivirine is given in combination with dasabuvir with ombitasvir/paritaprevir/ritonavir, with a consequent potential for QT-prolongation. If an HIV protease inhibitor is added (atazanavir, darunavir), rilpivirine exposure may increase even further and is therefore not recommended. Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring.

NNRTIs other than rilpivirine (efavirenz, etravirine, and nevirapine) are contraindicated (see section 4.3).

Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines

Paediatric population

The safety and efficacy of dasabuvir in children below 18 years have not been established. No data are available.

Lactose

Exviera contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Dasabuvir must always be administered together with ombitasvir/paritaprevir/ritonavir . When co-administered they exert mutual effects on each other (see section 5.2). Therefore, the interaction profile of the compounds must be considered as a combination.

Pharmacodynamic interactions

Coadministration with enzyme inducers may lead to an increased risk of adverse reactions and ALT elevations (see Table 2).
Coadministration with ethinylestradiol may lead to increased risk of ALT elevations (see sections 4.3 and 4.4). Contraindicated enzyme inducers are provided in section 4.3.

Pharmacokinetic interactions

Potential for Exviera to affect the pharmacokinetics of other medicinal products

In vivo drug interaction studies evaluated the net effect of the combination treatment, including ritonavir. The following section describes the specific transporters and metabolizing enzymes that are affected by dasabuvir when combined with ombitasvir/paritaprevir/ritonavir. See Table 2 for guidance regarding potential drug interactions and dosing recommendations for Exviera administered with ombitasvir/paritaprevir/ritonavir.

Medicinal products metabolised by CYP3A4
Refer to the ombitasvir/paritaprevir/ritonavir prescribing information for details. (see also Table 2).
Medicinal products transported by the OATP family
Refer to the ombitasvir/paritaprevir/ritonavir prescribing information for details on OATP1B1, OATP1B3 and OATP2B1 substrates (see also Table 2).

Medicinal products transported by BCRP
Dasabuvir is an inhibitor of BCRP *in vivo*. Co-administration of dasabuvir with ombitasvir/paritaprevir/ritonavir together with medicinal products that are substrates of BCRP may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring. Such medicinal products include sulfasalazine, imatinib and some of the statins (see Table 2). See also Table 2 for specific advice on rosuvastatin which has been evaluated in a drug interaction study.

Medicinal products transported by Pgp in the intestine
While dasabuvir is an in vitro inhibitor of P-gp, no significant change was observed in the exposure of the P-gp substrate, digoxin, when administered with Exviera with ombitasvir/paritaprevir/ritonavir. It may not be excluded that the systemic exposure of dabigatran etexilate is increased by dasabuvir due to inhibition of P-gp in the intestine.

Medicinal products metabolised by glucuronidation
Dasabuvir is an inhibitor of UGT1A1 *in vivo*. Co-administration of dasabuvir with medicinal products that are primarily metabolized by UGT1A1 result in increased plasma concentrations of such medicinal products; routine clinical monitoring is recommended for narrow therapeutic index medicinal products (i.e. levothyroxine). See also Table 2 for specific advice on raltegravir and buprenorphine which have been evaluated in drug interaction studies. Dasabuvir has also been found to inhibit UGT1A4, 1A6 and intestinal UGT2B7 *in vitro* at *in vivo* relevant concentrations.

Medicinal products metabolised by CYP2C19
Co-administration of dasabuvir with ombitasvir/paritaprevir/ritonavir can decrease exposures of medicinal products that are metabolized by CYP2C19 (e.g. lansoprazole, esomeprazole, s- mephenytoin), which may require dose adjustment/clinical monitoring. CYP2C19 substrates evaluated in drug interaction studies include omeprazole and escitalopram (Table 2).

Medicinal products metabolised by CYP2C9
Dasabuvir administered with ombitasvir/paritaprevir/ritonavir did not affect the exposures of the CYP2C9 substrate warfarin. Other CYP2C9 substrates (NSAIDs (e.g. ibuprofen), antidiabetics (e.g. glimepiride, glipizide) are not expected to require dose adjustments.

Medicinal products metabolised by CYP2D6 or CYP1A2
Dasabuvir administered with ombitasvir/paritaprevir/ritonavir did not affect the exposures of the CYP2D6 /CYP1A2 substrate duloxetine. Exposures of cyclobenzaprine, a CYP1A2 substrate, were decreased. Clinical monitoring and dose adjustment may be needed for other CYP1A2 substrates (e.g. ciprofloxacin, cyclobenzaprine, theophylline and caffeine).CYP2D6 substrates (e.g. desipramine, metoprolol and dextromethorphan) are not expected to require dose adjustments.

Medicinal products renally excreted via transport proteins
Dasabuvir does not inhibit organic anion transporter (OAT1) *in vivo* as shown by the lack of interaction with tenofovir (OAT1 substrate). *In vitro* studies show that dasabuvir is not an inhibitor of organic cation transporters (OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations.

Therefore, dasabuvir is not expected to affect medicinal products which are primarily excreted by the renal route via these transporters (see section 5.2).

<u>Potential for other medicinal products to affect the pharmacokinetics of dasabuvir</u>

Medicinal products that inhibit CYP2C8
Co-administration of dasabuvir with medicinal products that inhibit CYP2C8 (e.g. teriflunomide, deferasirox) may increase dasabuvir plasma concentrations. Strong CYP2C8 inhibitors are contraindicated with dasabuvir (see section 4.3 and Table 2).

Enzyme inducers
Co-administration of dasabuvir with medicinal products that are moderate or strong enzyme inducers is expected to decrease dasabuvir plasma concentrations and reduce its therapeutic effect. Contraindicated enzyme inducers are provided in section 4.3 and Table 2.

Dasabuvir is a substrate of P-gp and BCRP and its major metabolite M1 is a substrate of OCT1 *in vitro*. Inhibition of P-gp and BCRP is not expected to show clinically relevant increases in exposures of dasabuvir (Table 2).

Dasabuvir M1 metabolite was quantified in all the drug interaction studies. Changes in exposures of the metabolite were generally consistent with that observed with dasabuvir except for studies with CYP2C8 inhibitor, gemfibrozil, where the metabolite exposures decreased by up to 95% and CYP3A inducer, carbamazepine, where the metabolite exposures decreased by only up to 39%.

Patients treated with vitamin K antagonists

As liver function may change during treatment with Exviera administered with ombitasvir/paritaprevir/ritonavir, a close monitoring of International Normalised Ratio (INR) values is recommended.

Drug interaction studies

Recommendations for co-administration of Exviera with ombitasvir/paritaprevir/ritonavir for a number of medicinal products are provided in Table 2.

If a patient is already taking medicinal product(s) or initiating a medicinal product while receiving Exviera and ombitasvir/paritaprevir/ritonavir for which potential for drug interaction is expected, dose adjustment of the concomitant medicinal product(s) or appropriate clinical monitoring should be considered (Table 2).

If dose adjustments of concomitant medicinal products are made due to treatment with Exviera and ombitasvir/paritaprevir/ritonavir, doses should be re-adjusted after administration of Exviera and ombitasvir/paritaprevir/ritonavir is completed.

Table 2 provides the Least Squares Means Ratio (90% Confidence Interval) effect on concentration of dasabuvir and ombitasvir/paritaprevir/ritonavir and concomitant medicinal products.
The direction of the arrow indicates the direction of the change in exposures (C_{max}, and AUC) in the paritaprevir, ombitasvir, dasabuvir and the co-administered medicinal product (↑= *increase more than 20%,* ↓ *= decrease more than 20%,* ↔ *= no change or change less than 20%*).

This is not an exclusive list. Exviera is administered with ombitasvir/paritaprevir/ritonavir. For interactions with ombitasvir/ paritaprevir /ritonavir refer to the prescribing information.

Table 2. Interactions between Exviera with ombitasvir/paritaprevir/ritonavir and other medicinal products

Medicinal Product/ Possible Mechanism of Interaction	**GIVEN WITH**	**EFFECT**	**C_{max}**	**AUC**	**C_{trough}**	**Clinical Comments**
AMINOSALICYLATE						
Sulfasalazine Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not Studied. Expected: ↑ sulfasalazine				Caution should be used when sulfasalazine is co-administered with Exviera + ombitasvir/paritaprevir/ritonavir.

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
ANTIARRYTHMICS						
Digoxin 0.5 mg single dose Mechanism: P-gp inhibition by dasabuvir, paritaprevir, and ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ digoxin	1.15 (1.04-1.27)	1.16 (1.09-1.23)	1.01 (0.97-1.05)	While no dose adjustment is necessary for digoxin, appropriate monitoring of serum digoxin levels is recommended.
		↔ 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)	
ANTIBIOTICS (SYSTEMIC ADMINISTRATION)						
Sulfameth-oxazole, trimethoprim 800/160 mg twice daily Mechanism: increase in dasabuvir possibly due to CYP2C8 inhibition by trimethoprim	Exviera + ombitasvir/ paritaprevir/ ritonavir	↑ Sulfameth-oxazole,	1.21 (1.15-1.28)	1.17 (1.14-1.20)	1.15 (1.10-1.20)	No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↑ trimethoprim	1.17 (1.12-1.22)	1.22 (1.18-1.26)	1.25 (1.19-1.31)	
		↑ dasabuvir	1.15 (1.02-1.31)	1.33 (1.23-1.44)	NA	
		↔ ombitasvir	0.88 (0.83-0.94)	0.85 (0.80-0.90)	NA	
		↓ paritaprevir	0.78 (0.61-1.01)	0.87 (0.72-1.06)	NA	
ANTICANCER AGENTS						
Enzalutamide Mitotane Mechanism: CYP3A4 induction by enzalutamide or mitotane.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↓ dasabuvir ↓ombitasvir ↓ paritaprevir				Concomitant use is contraindicated (see section 4.3).
Imatinib Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not Studied. Expected: ↑ imatinib				Clinical monitoring and lower doses of imatinib are recommended.
ANTICOAGULANTS						
Warfarin	Exviera + ombitasvir/ paritaprevir	↔ R-warfarin	1.05 (0.95-1.17)	0.88 (0.81-0.95)	0.94 (0.84-1.05)	While no change in the pharmacokinetics of warfarin is expected, close monitoring of INR is

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
5 mg single dose and other vitamin K antagonists	/ritonavir	↔ S-warfarin	0.96 (0.85-1.08)	0.88 (0.81-0.96)	0.95 (0.88-1.02)	recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Exviera + ombitasvir/paritaprevir/ritonavir
		↔ 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)	
Dabigatran etexilate Mechanism: Intestinal P-gp inhibition by paritaprevir and ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not Studied. Expected: ↑ dabigatran etexilate				Exviera + ombitasvir/paritaprevir/ritonavir may increase the plasma concentrations of dabigatran etexilate. Use with caution.
ANTICONVULSANTS						
carbamaze-pine 200 mg once daily followed by 200 mg twice daily Mechanism: CYP3A4 induction by carbamazepine.	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ carba-mazepine	1.10 (1.07-1.14)	1.17 (1.13-1.22)	1.35 (1.27-1.45)	Concomitant use is contraindicated (see section 4.3).
		↓ carbamaze pine 10, 11-epoxide	0.84 (0.82-0.87)	0.75 (0.73-0.77)	0.57 (0.54-0.61)	
		↓ dasabuvir	0.45 (0.41-0.50)	0.30(0.27-0.33)	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	
Phenobarbital Mechanism: CYP3A4 induction by phenobarbital.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↓ dasabuvir ↓ paritaprevir ↓ ombitasvir				Concomitant use is contraindicated (see section 4.3).
Phenytoin Mechanism: CYP3A4 induction by phenytoin.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↓ dasabuvir ↓ paritaprevir ↓ ombitasvir				Concomitant use is contraindicated (see section 4.3).

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
S-mephenytoin Mechanism: CYP2C19 induction by ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↓ S-mephenytoin				Clinical monitoring and dose adjustment maybe needed for s-mephenytoin.
ANTIDEPRESSANTS						
Escitalopram 10 mg single dose	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ es-citalopram	1.00 (0.96-1.05)	0.87 (0.80-0.95)	NA	No dose adjustment is necessary for escitalopram.
		↑ S-Desmethyl citalopram	1.15 (1.10-1.21)	1.36 (1.03-1.80)	NA	
		↔ dasabuvir	1.10 (0.95-1.27)	1.01 (0.93-1.10)	0.89 (0.79-1.00)	
		↔ ombitasvir	1.09 (1.01-1.18)	1.02 (1.00-1.05)	0.97 (0.92-1.02)	
		↔ paritaprevir	1.12 (0.88-1.43)	0.98 (0.85-1.14)	0.71 (0.56-0.89)	
Duloxetine 60 mg single dose	Exviera + ombitasvir/ paritaprevir /ritonavir	↓ duloxetine	0.79 (0.67-0.94)	0.75 (0.67-0.83)	NA	No dose adjustment is necessary for duloxetine. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	0.94 (0.81-1.09)	0.92 (0.81-1.04)	0.88 (0.76-1.01)	
		↔ ombitasvir	0.98 (0.88-1.08)	1.00 (0.95-1.06)	1.01 (0.96-1.06)	
		↓ paritaprevir	0.79 (0.53-1.16)	0.83 (0.62-1.10)	0.77 (0.65-0.91)	
ANTIFUNGALS						
Ketoconazole 400 mg once daily Mechanism: CYP3A4/P-gp inhibition by ketoconazole and paritaprevir/ ritonavir/ ombitasvir	Exviera + ombitasvir/ paritaprevir / ritonavir	↑ keto-conazole	1.15 (1.09-1.21)	2.17 (2.05-2.29)	NA	Concomitant use is contraindicated (see the prescribing information for ombitasvir/paritaprevir/ ritonavir).
		↑ 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	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
ANTIHYPERLIPIDAEMICS						
Gemfibrozil 600 mg twice daily Mechanism: Increase in dasabuvir exposure is due to CYP2C8 inhibition and increase in paritaprevir is possibly due to OATP1B1 inhibition by gemfibrozil.	Exviera + paritaprevir / ritonavir	↑ dasabuvir	2.01 (1.71-2.38)	11.25 (9.05-13.99)	NA	Concomitant use is contraindicated (see section 4.3).
		↑ paritaprevir	1.21 (0.94-1.57)	1.38 (1.18-1.61)	NA	
ANTIMYCOBACTERIALS						
Rifampicin Mechanism: CYP3A4/CYP 2C8 induction by rifampicin.	Exviera + Ombitasvir /paritaprevi r /ritonavir	Not Studied. Expected: ↓ dasabuvir ↓ ombitasvir ↓ paritaprevir				Concomitant use is contra-indicated (see section 4.3).
BIGUANIDE ORAL ANTIHYPERGLYCEMICS						
Metformin 500 mg single dose	Exviera +ombitasvi r/paritaprev ir/ritonavir	↓ metformi n	0.77 (0.71-0.83)	0.90 (0.84-0.97)	NA	No dose adjustment needed for metformin when co-administered with Exviera + ombitasvir/paritaprevir/rito navir.
		↔ dasabuvir	0.83 (0.74-0.93)	0.86 (0.78-0.94)	0.95 (0.84-1.07)	
		↔ ombitasvi r	0.92 (0.87-0.98)	1.01 (0.97-1.05)	1.01 (0.98-1.04)	
		↓ paritaprev ir	0.63 (0.44-0.91)	0.80 (0.61-1.03)	1.22 (1.13-1.31)	
CALCIUM CHANNEL BLOCKERS						
Amlodipine 5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ amlodipine	1.26 (1.11-1.44)	2.57 (2.31-2.86)	NA	Decrease in amlodipine dose by 50% and monitor patients for clinical effects.
		↔ 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
		↓ paritaprevir	0.77 (0.64-0.94)	0.78 (0.68-0.88)	0.88 (0.80-0.95)	
CONTRACEPTIVES						
ethinylestradiol/ norgestimate 0.035/0.25 mg once daily Mechanism: possibly due to UGT inhibition by paritaprevir, ombitasvir and dasabuvir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ ethinyl estradiol	1.16 (0.90-1.50)	1.06 (0.96-1.17)	1.12 (0.94-1.33)	Ethinylestradiol containing oral contraceptives are contraindicated (see section 4.3).
		Norgestimate metabolites:				
		↑ norgestrel	2.26 (1.91-2.67)	2.54 (2.09-3.09)	2.93 (2.39-3.57)	
		↑ nor-elgestromine	2.01 (1.77-2.29)	2.60 (2.30-2.95)	3.11 (2.51-3.85)	
		↓ 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)	
nor-ethindrone (progestin only pill) 0.35 mg once daily	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ nor-ethindrone	0.83 (0.69-1.01)	0.91 (0.76-1.09)	0.85 (0.64-1.13)	No dose adjustment is necessary for norethindrone or Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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)	
DIURETICS						
Furosemide 20 mg single dose Mechanism: possibly due to UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ furosemide	1.42 (1.17-1.72)	1.08 (1.00-1.17)	NA	Monitor patients for clinical effects; a decrease in furosemide dose of up to 50% may be required. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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)	
HCV ANTIVIRAL						
Sofosbuvir 400 mg once daily	Exviera + ombitasvir/ paritaprevir/	↑ sofosbuvir	1.61 (1.38-1.88)	2.12 (1.91-2.37)	NA	No dose adjustment needed for sofosbuvir when administered with

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Mechanism: BCRP and P-gp inhibition by paritaprevir, ritonavir and dasabuvir	ritonavir	↑ GS-331007	1.02 (0.90-1.16)	1.27 (1.14-1.42)	NA	Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	1.09 (0.98-1.22)	1.02 (0.95-1.10)	0.85 (0.76-0.95)	
		↔ ombitasvir	0.93 (0.84-1.03)	0.93 (0.87-0.99)	0.92 (0.88-0.96)	
		↔ paritaprevir	0.81 (0.65-1.01)	0.85 (0.71-1.01)	0.82 (0.67-1.01)	
HERBAL PRODUCTS						
St. John's Wort (*hypericum perforatum*) Mechanism: CYP3A4 induction by St. John's Wort.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not Studied. Expected: ↓ dasabuvir ↓ ombitasvir ↓ paritaprevir				Concomitant use is contraindicated (see section 4.3).
HIV ANTIVIRALS: PROTEASE INHIBITORS For a general comment on treatment of HIV co-infected patients, including a discussion on different antiretroviral regimens that may be used, please see section 4.4 (Treatment of HIV co-infected patients) and the prescribing information of ombitasvir/ paritaprevir /ritonavir.						
Atazanavir 300 mg once daily (given at the same time) Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATPs by atazanavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ atazanavir	0.91 (0.84-0.99)	1.01 (0.93-1.10)	0.90 (0.81-1.01)	The recommended dose of atazanavir is 300 mg, without ritonavir, in combination with Exviera + ombitasvir/paritatprevir/ritonavir. Atazanavir must be administered at the same time as Exviera +ombitasvir/paritaprevir/ritonavir. Ritonavir dose in ombitasvir/paritaprevir/ritonavir will provide atazanavir pharmacokinetic enhancement. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir. The combination of atazanavir and ombitasvir/paritaprevir/ritonavir + dasabuvir increase bilirubin levels, in particular when ribavirin is part of the hepatitis C regimen, see sections 4.4 and 4.8.
		↔ dasabuvir	0.83 (0.71-0.96)	0.82 (0.71-0.94)	0.79 (0.66-0.94)	
		↓ ombitasvir	0.77 (0.70-0.85)	0.83 (0.74-0.94)	0.89 (0.78-1.02)	
		↑ paritaprevir	1.46 (1.06-1.99)	1.94 (1.34-2.81)	3.26 (2.06-5.16)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Atazanavir/ ritonavir 300/100 mg once daily (administered in the evening) Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir and CYP3A inhibition by the additional dose of ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ atazanavir	1.02 (0.92-1.13)	1.19 (1.11-1.28)	1.68 (1.44-1.95)	
		↔ 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)	
Darunavir 800 mg once daily (given at the same time) Mechanism: Unknown	Exviera + ombitasvir/ paritaprevir /ritonavir	↓ darunavir	0.92 (0.87-0.98)	0.76 (0.71-0.82)	0.52 (0.47-0.58)	The recommended dose of darunavir is 800 mg once daily, without ritonavir, when administered at the same time as ombitasvir/paritaprevir/ritonavir + dasabuvir (ritonavir dose in ombitasvir/paritaprevir/ritonavir will provide darunavir pharmacokinetic enhancement). This regimen can be used in the absence of extensive PI resistance (i.e. lack of darunavir associated RAMs), see also section 4.4. . Darunavir combined with ombitasvir/paritaprevir/ritonavir + dasabuvir is not recommended in patients with extensive PI resistance. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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)	
Darunavir/	Exviera + ombitasvir/ paritaprevir	↔ darunavir	0.87 (0.79-0.96)	0.80 (0.74-0.86)	0.57 (0.48-0.67)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
ritonavir 600/100 mg twice daily Mechanism: Unknown	/ritonavir	↓ 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)	
Darunavir/ ritonavir 800/100 mg once daily (administered in the evening) Mechanism: Unknown	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ darunavir	0.79 (0.70-0.90)	1.34 (1.25-1.43)	0.54 (0.48-0.62)	
		↓ 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)	
lopinavir / ritonavir 400/100 mg twice daily[1] Mechanism: Increase in paritaprevir exposures may be due to inhibition of CYP3A/efflux transporters by lopinavir and higher dose of ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ lopinavir	0.87 (0.76-0.99)	0.94 (0.81-1.10)	1.15 (0.93-1.42)	Lopinavir/ritonavir 400/100 mg twice daily or 800/200 mg once daily is contraindicated with dasabuvir and ombitasvir/paritaprevir/ritonavir due to increase in paritaprevir exposures (see prescribing information of ombitasvir/paritaprevir/ritonavir).
		↔ 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)	
HIV ANTIVIRALS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS						
Rilpivirine[2] 25 mg once daily administered in the morning, with	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ rilpivirine	2.55 (2.08-3.12)	3.25 (2.80-3.77)	3.62 (3.12-4.21)	Co-administration of Exviera and ombitasvir/paritaprevir/ritonavir with rilpivirine once daily should only be considered in patients without known QT-prolongation, and without other QT-prolongation co-administered medicinal products. If the combination is used, repeated ECG-monitoring should be done, see
		↔ 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
food Mechanism: CYP3A inhibition by ritonavir.		↑ paritaprevir	1.30 (0.94-1.81)	1.23 (0.93-1.64)	0.95 (0.84-1.07)	section 4.4. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate 600/300/200 mg once daily Mechanism: possible enzyme induction by efavirenz.	Exviera + ombitasvir/ paritaprevir /ritonavir	Co-administration of efavirenz (enzyme inducer) based regimens with paritaprevir /ritonavir + dasabuvir resulted in ALT elevations and therefore, early discontinuation of the study.				Concomitant use with efavirenz containing regimens is contraindicated (see section 4.3).
Nevirapine etravirine	Exviera + ombitasvir/ paritaprevir /ritonavir	Not Studied. Expected: ↓ dasabuvir ↓ ombitasvir ↓ paritaprevir				Concomitant use is contraindicated (see section 4.3).
HIV ANTIVIRALS: INTEGRASE STRAND TRANSFER INHIBITOR						
Dolutegravir 50 mg once daily Mechanism: possibly due to UGT1A1 inhibition by paritaprevir, dasabuvir and ombitasvir and CYP3A4 inhibition by ritonavir	Exviera + ombitasvir/paritaprevir/ritonavir	↑ dolutegravir	1.22 (1.15-1.29)	1.38 (1.30-1.47)	1.36 (1.19-1.55)	No dose adjustment needed for dolutegravir when administered with Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	1.01 (0.92-1.11)	0.98 (0.92-1.05)	0.92 (0.85-0.99)	
		↔ ombitasvir	0.96 (0.89-1.03)	0.95 (0.90-1.00)	0.92 (0.87-0.98)	
		↔ paritaprevir	0.89 (0.69-1.14)	0.84 (0.67-1.04)	0.66 (0.59-0.75)	
Raltegravir	Exviera + ombitasvir/ paritaprevir	↑ raltegravir	2.33 (1.66-3.27)	2.34 (1.70-3.24)	2.00 (1.17-3.42)	No dose adjustment is necessary for raltegravir or Exviera +

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
400 mg twice daily Mechanism: UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	/ritonavir	No clinically relevant changes in dasabuvir, paritaprevir, and ombitasvir exposures (based on comparison with historical data) were observed during the co-administration.				ombitasvir/paritaprevir/ritonavir.
HIV ANTIVIRALS: NUCLEOSIDE INHIBITORS						
Abacavir/ lamivudine 600/300 mg once daily	Exviera + ombitasvir/paritaprevir/ritonavir	↔ abacavir	0.87 (0.78-0.98)	0.94 (0.90-0.99)	NA	No dose adjustment needed for abacavir or lamivudine when administered with Exviera + ombitasvir/paritaprevir/ritonavir.
		↓ lamivudine	0.78 (0.72-0.84)	0.88 (0.82-0.93)	1.29 (1.05-1.58)	
		↔ dasabuvir	0.94 (0.86-1.03)	0.91 (0.86-0.96)	0.95 (0.88-1.02)	
		↔ ombitasvir	0.82 (0.76-0.89)	0.91 (0.87-0.95)	0.92 (0.88-0.96)	
		↔ paritaprevir	0.84 (0.69-1.02)	0.82 (0.70-0.97)	0.73 (0.63-0.85)	
Em-tricitabine/ tenofovir 200 mg once daily/300 mg once daily	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ em-tricitabine	1.05 (1.00-1.12)	1.07 (1.00-1.14)	1.09 (1.01-1.17)	No dose adjustment is necessary for emtricitabine/tenofovir and Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ tenofovir	1.07 (0.93-1.24)	1.13 (1.07-1.20)	1.24 (1.13-1.36)	
		↔ dasabuvir	0.85 (0.74-0.98)	0.85 (0.75-0.96)	0.85 (0.73-0.98)	
		↔ ombitasvir	0.89 (0.81-0.97)	0.99 (0.93-1.05)	0.97 (0.90-1.04)	
		↓ paritaprevir	0.68 (0.42-1.11)	0.84 (0.59-1.17)	1.06 (0.83-1.35)	
HMG CoA REDUCTASE INHIBITOR						
Rosuvastatin 5 mg once daily Mechanism: OATP1B inhibition by	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ rosuvastatin	7.13 (5.11-9.96)	2.59 (2.09-3.21)	0.59 (0.51-0.69)	The maximum daily dose of rosuvastatin should be 5 mg (see section 4.4). No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
paritaprevir and BCRP inhibition by dasabuvir paritaprevir, and ritonavir.		↑ paritaprevir	1.59 (1.13-2.23)	1.52 (1.23-1.90)	1.43 (1.22-1.68)	
Pravastatin 10 mg once daily Mechanism: OATP1B1 inhibition by paritaprevir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ pravastatin	1.37 (1.11-1.69)	1.82 (1.60-2.08)		Reduce pravastatin dose by 50%. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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)	0.94 (0.89-0.99)	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)	
Fluvastatin Mechanism: OATP1B/BCRP inhibition by paritaprevir. Pitavastatin Mechanism: OATP1B inhibition by paritaprevir.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↑ fluvastatin ↑ pitavastatin ↔ dasabuvir ↔ ombitasvir ↔ paritaprevir				Concomitant use with fluvastatin and pitavastatin is not recommended (see section 4.4). A temporary suspension of fluvastatin and pitavastatin is recommended for the duration of treatment. If statin treatment is required during the treatment period, a switch to dose reduced pravastatin or rosuvastatin is possible. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
IMMUNOSUPPRESSANTS						
Ciclosporin 30 mg once daily single dose[3] Mechanism:	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ ciclosporin	1.01 (0.85-1.20)	5.82 (4.73-7.14)	15.8 (13.8-18.09)	When starting co-administration with Exviera and ombitasvir/paritaprevir/ritonavir, give one fifth of the total daily dose of ciclosporin once daily with ombitasvir/ paritaprevir /ritonavir. Monitor ciclosporin levels and adjust dose and/or dosing frequency as needed.
		↓ dasabuvir	0.66 (0.58-0.75)	0.70 (0.65-0.76)	0.76 (0.71-0.82)	
		↔ ombitasvir	0.99 (0.92-1.07)	1.08 (1.05-1.11)	1.15 (1.08-1.23)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Effect on ciclosporin is due to CYP3A4 inhibition by ritonavir and increase in paritaprevir exposures may be due to OATP/BCRP/ P-gp inhibition by ciclosporin.		↑ paritaprevir	1.44 (1.16-1.78)	1.72 (1.49-1.99)	1.85 (1.58-2.18)	No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
Everolimus 0.75 mg single dose Mechanism: Effect on everolimus is due to CYP3A4 inhibition by ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ everolimus	4.74 (4.29-5.25)	27.1 (24.5-30.1)	16.1 (14.5-17.9)[4]	Co-administration of Exviera + ombitasvir/paritaprevir/ritonavir with everolimus is not recommended because of a significant increase in everolimus exposures which cannot be properly dose adjusted with available dose strengths.
		↔ dasabuvir	1.03 (0.90-1.18)	1.08 (0.98-1.20)	1.14 (1.05-1.23)	
		↔ ombitasvir	0.99 (0.95-1.03)	1.02 (0.99-1.05)	1.02 (0.99-1.06)	
		↔ paritaprevir	1.22 (1.03-1.43)	1.26 (1.07-1.49)	1.06 (0.97-1.16)	
Sirolimus 0.5 mg single dose[5] Mechanism: Effect on sirolimus is due to CYP3A4 inhibition by ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ Sirolimus	6.40 (5.34-7.68)	38.0 (31.5-45.8)	19.6 (16.7-22.9)[6]	Concomitant use of sirolimus with Exviera + ombitasvir/paritaprevir/ritonavir is not recommended unless the benefits outweigh the risks (see section 4.4). If sirolimus is used together with Exviera + ombitasvir/paritaprevir/ritonavir, administer sirolimus 0.2 mg twice a week (every 3 or 4 days on the same two days each week). Sirolimus blood concentrations should be monitored every 4 to 7 days until 3 consecutive trough levels have shown stable concentrations of sirolimus. Sirolimus dose and/or dosing frequency should be adjusted as needed. 5 days after completion of Exviera + ombitasvir/paritaprevir/ritonavir treatment, the sirolimus dose and dosing frequency prior to receiving Exviera + ombitasvir/paritaprevir/ritonavir should be resumed, along with routine monitoring of sirolimus blood concentrations.
		↔ dasabuvir	1.04 (0.89-1.22)	1.07 (0.95-1.22)	1.13 (1.01-1.25)	
		↔ ombitasvir	1.03 (0.93-1.15)	1.02 (0.96-1.09)	1.05 (0.98-1.12)	
		↔ paritaprevir	1.18 (0.91-1.54)	1.19 (0.97-1.46)	1.16 (1.00-1.34)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Tacrolimus 2 mg single dose[7] Mechanism: Effect on tacrolimus is due to CYP3A4 inhibition by ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ tacrolimus	3.99 (3.21-4.97)	57.1 (45.5-71.7)	16.6 (13.0-21.2)	Concomitant use of tacrolimus with Exviera and ombitasvir/paritaprevir/ritonavir is not recommended unless the benefits outweigh the risks (see section 4.4). If tacrolimus with Exviera and ombitasvir/paritaprevir/ritonavir are used concomitantly, tacrolimus should not be administered on the day Exviera and ombitasvir/paritaprevir/ritonavir are initiated. Beginning the day after Exviera and ombitasvir/paritaprevir/ritonavir are initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. The recommended tacrolimus dosing is 0.5 mg every 7 days. Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with Exviera and ombitasvir/paritaprevir/ritonavir and the dose and/or dosing frequency should be adjusted as needed. Upon completion of Exviera and ombitasvir/paritaprevir/ritonavir treatment, the appropriate dose and dosing frequency of tacrolimus should be guided by assessment of tacrolimus blood concentrations.
		↔ 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)	
IRON CHELATORS						
Deferasirox	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↑ dasabuvir				Deferasirox may increase dasabuvir exposures and should be used with caution.
MEDICINAL PRODUCTS USED IN MULTIPLE SCLEROSIS						
Teriflunomide	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↑ dasabuvir				Teriflunomide may increase dasabuvir exposures and should be used with caution.
OPIOIDS						
Methadone 20-120 mg once daily[8]	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ R-Methadone	1.04 (0.98-1.11)	1.05 (0.98-1.11)	0.94 (0.87-1.01)	No dose adjustment is necessary for methadone and Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ S-Methadone	0.99 (0.91-1.08)	0.99 (0.89-1.09)	0.86 (0.76-0.96)	
		↔ ombitasvir/paritaprevir and dasabuvir (based on the cross-study comparison)				
buprenorphine	Exviera +	↑ bu-	2.18	2.07	3.12	No dose adjustment is necessary for

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
/ naloxone 4-24 mg/1-6 mg once daily[8] Mechanism: CYP3A4 inhibition by ritonavir and UGT inhibition by paritaprevir, ombitasvir and dasabuvir.	ombitasvir/ paritaprevir /ritonavir	prenorphine	(1.78-2.68)	(1.78-2.40)	(2.29-4.27)	buprenorphine/naloxone and Exviera + ombitasvir/paritaprevir/ritonavir.
		↑ norbu-prenorphine	2.07 (1.42-3.01)	1.84 (1.30-2.60)	2.10 (1.49-2.97)	
		↑ naloxone	1.18 (0.81-1.73)	1.28 (0.92-1.79)	NA	
		↔ ombitasvir /paritaprevir and dasabuvir (based on the cross-study comparison)				
MUSCLE RELAXANTS						
Carisoprodol 250 mg single dose Mechanism: CYP2C19 induction by ritonavir	Exviera + ombitasvir/ paritaprevir/ ritonavir	↓ Carisoprodol	0.54 (0.47-0.63)	0.62 (0.55-0.70)	NA	No dose adjustment required for carisoprodol; increase dose if clinically indicated.
		↔ 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)	
Cyclobenzaprine 5 mg single dose Mechanism: decrease possibly due to CYP1A2 induction by ritonavir	Exviera + ombitasvir/ paritaprevir/ ritonavir	↓ cyclobenzaprine	0.68 (0.61-0.75)	0.60 (0.53-0.68)	NA	No dose adjustment for cyclobenzaprine required; increase dose if clinically indicated.
		↔ 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)	
NARCOTIC ANALGESICS						
Paracetamol (given as fixed dose hydrocodone/ paracetamol) 300 mg single dose	Exviera + ombitasvir/ paritaprevir/ ritonavir	↔ Paracetamol	1.02 (0.89-1.18)	1.17 (1.09-1.26)	NA	No dose adjustment is necessary for paracetamol when administered with Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
		↔ paritaprevir	1.01 (0.80-1.27)	1.03 (0.89-1.18)	1.10 (0.97-1.26)	
Hydrocodone (as given in a fixed-dose hydrocodone/ paracetamol) 5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir	Exviera + ombitasvir /paritaprevir /ritonavir	↑ hydrocodone	1.27 (1.14-1.40)	1.90 (1.72 - 2.10)	NA	A reduction of hydrocodone dose by 50% and/or clinical monitoring should be considered when administered with Exviera+ ombitasvir/paritaprevir/ritonavir.
		Changes for dasabuvir and ombitasvir, paritaprevir are the same as shown for paracetamol above				
PROTON PUMP INHIBITORS						
Omeprazole 40 mg once daily Mechanism: CYP2C19 induction by ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↓ omeprazole	0.62 (0.48-0.80)	0.62 (0.51-0.75)	NA	If clinically indicated, higher doses of omeprazole should be used. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	1.13 (1.03-1.25)	1.08 (0.98-1.20)	1.05 (0.93-1.19)	
		↔ 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)	
Esomeprazole Lansoprazole Mechanism: CYP2C19 induction by ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↓ esomeprazole, lansoprazole				If clinically indicated, higher doses of esomeprazole/lansoprazole may be needed.
SEDATIVES / HYPNOTICS						
Zolpidem 5 mg single dose	Exviera + ombitasvir/ paritaprevir /ritonavir	↔ zolpidem	0.94 (0.76-1.16)	0.95 (0.74-1.23)	NA	No dose adjustment is necessary for zolpidem. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	0.93 (0.84-1.03)	0.95 (0.84-1.08)	0.92 (0.83-1.01)	
		↔ ombitasvir	1.07 (1.00-1.15)	1.03 (1.00-1.07)	1.04 (1.00-1.08)	
		↓ paritaprevir	0.63 (0.46-0.86)	0.68 (0.55-0.85)	1.23 (1.10-1.38)	
Diazepam 2 mg single dose Mechanism: CYP2C19 induction by	Exviera + ombitasvir/ paritaprevir/ ritonavir	↓diazepam	1.18 (1.07-1.30)	0.78 (0.73-0.82)	NA	No dose adjustment required for diazepam; increase dose if clinically indicated.
		↓ nordiazepam	1.10 (1.03-1.19)	0.56 (0.45-0.70)	NA	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
ritonavir		↔ dasabuvir	1.05 (0.98-1.13)	1.01 (0.94-1.08)	1.05 (0.98-1.12)	
		↔ ombitasvir	1.00 (0.93-1.08)	0.98 (0.93-1.03)	0.93 (0.88-0.98)	
		↔ paritaprevir	0.95 (0.77-1.18)	0.91 (0.78-1.07)	0.92 (0.82-1.03)	
Alprazolam 0.5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir.	Exviera + ombitasvir/ paritaprevir /ritonavir	↑ alprazolam	1.09 (1.03-1.15)	1.34 (1.15-1.55)	NA	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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)	
THYROID HORMONES						
Levothyroxine Mechanism: UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	Exviera + ombitasvir/ paritaprevir /ritonavir	Not studied. Expected: ↑ levothyroxine				Clinical monitoring and dose adjustment may be required for levothyroxine.

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments

1. Lopinavir/ritonavir 800/200 mg once daily (administered in the evening) was also administered with dasabuvir with ombitasvir/paritaprevir/ritonavir. The effect on C_{max} and AUC of DAAs and lopinavir was similar to that observed when lopinavir/ritonavir 400/100 mg twice daily was administered with dasabuvir and ombitasvir/paritaprevir/ritonavir.
2. Rilpivirine was also administered with food in the evening and 4 hours after dinner with Exviera + ombitasvir/paritaprevir/ritonavir in the study. The effect on rilpivirine exposures was similar to that observed when rilpivirine was administered in the morning with food with Exviera + ombitasvir/paritaprevir/ritonavir.
3. Ciclosporin 100 mg dosed alone and 30 mg administered with Exviera + ombitasvir/paritaprevir/ritonavir. Dose normalized cyclosporine ratios are shown for interaction with Exviera + ombitasvir/paritaprevir/ritonavir.
4. C_{12}:= concentration at 12 hours following single dose of everolimus.
5. Sirolimus 2 mg was dosed alone, 0.5 mg administered with Exviera + ombitasvir/paritaprevir/ritonavir. Dose normalized sirolimus ratios are shown for interaction with ombitasvir/paritaprevir/ritonavir + Exviera.
6. C_{24}:= concentration at 24 hours following single dose of cyclosporine, tacrolimus or sirolimus.
7. Tacrolimus 2 mg was dosed alone and 2 mg was administered with Exviera + ombitasvir/paritaprevir/ritonavir. Dose normalized tacrolimus ratios are shown for interaction with Exviera + ombitasvir/paritaprevir/ritonavir.
8. Dose normalised parameters reported for methadone, buprenorphine and naloxone.

Note: Doses used for Exviera + ombitasvir/paritaprevir/ritonavir were: ombitasvir 25 mg, paritaprevir 150 mg, ritonavir 100 mg, once daily and dasabuvir 400 mg twice daily or 250 mg twice daily. The dasabuvir exposures obtained with the 400 mg formulation and the 250 mg tablet are similar. Exviera + ombitasvir/paritaprevir/ritonavir was administered as multiple doses in all the drug interaction studies except the drug interaction studies with carbamazepine, gemfibrozil, ketoconazole, and sulfamethoxazole/trimethoprim.

Paediatric population

Drug interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential /contraception in males and females

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients when Exviera is used 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 the male partners of women who are pregnant. Refer to the Prescribing Information for ribavirin for additional information.

Female patients: Women of childbearing potential should not receive ribavirin unless they are using an effective form of contraception during treatment with ribavirin and for 4 months after treatment.

Male patients and their female partners: Either male patients or their female partners of childbearing potential must use a form of effective contraception during treatment with ribavirin and for 7 months after treatment.
Ethinylestradiol is contraindicated in combination with Exviera (see section 4.3). See additional information on specific hormonal contraceptives in sections 4.3 and 4.4.
Pregnancy

There are very limited data from the use of Exviera in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Exviera during pregnancy.

If ribavirin is co-administered with Exviera and ombitasvir/paritaprevir/ritonavir, the contraindications regarding use of ribavirin during pregnancy apply (see also the prescribing information of ribavirin).

Breast-feeding

It is not known whether dasabuvir and metabolites are excreted in human breast milk. Available pharmacokinetic data in animals have shown excretion of dasabuvir and metabolites in milk (see section 5.3). Because of the potential for adverse reactions from the medicinal product in breastfed infants, a decision must be made whether to discontinue breastfeeding or discontinue treatment with Exviera, taking into account the importance of the therapy to the mother. Patients receiving ribavirin should also refer to the prescribing information of ribavirin.

Fertility

No human data on the effect of dasabuvir on fertility are available. Animal studies do not indicate harmful effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that fatigue has been reported during treatment with Exviera in combination with ombitasvir/paritaprevir/ritonavir and ribavirin (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety summary is based on pooled data from phase 2 and 3 clinical trials in more than 2,600 subjects who received Exviera and ombitasvir/paritaprevir/ritonavir with or without ribavirin.

In subjects receiving Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin, the most commonly reported adverse reactions (greater than 20% of subjects) were fatigue and nausea. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.2% (5/2,044) and 4.8% (99/2,044) of subjects had ribavirin dose reductions due to adverse reactions.

In subjects receiving Exviera and ombitasvir/paritaprevir/ritonavir without ribavirin, adverse events typically associated to ribavirin (e.g. nausea, insomnia, anaemia) were less frequent and no subjects (0/588) permanently discontinued treatment due to adverse reactions.

The safety profile of Exviera and ombitasvir/paritaprevir/ritonavir was similar in patients without cirrhosis, and with compensated cirrhosis, with exception of increased rates of transient hyperbilirubinemia when ribavirin was part of the regimen.

Tabulated list of adverse reactions

Table 3 lists adverse reactions for which a causal relationship between dasabuvir, in combination with ombitasvir/paritaprevir/ritonavir, with or without ribavirin, and the adverse event is at least a reasonable possibility. The majority of adverse reactions presented in Table 3 were of grade 1 severity in Exviera- and ombitasvir/paritaprevir/ritonavir-containing regimens.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000).

Table 3. Adverse reactions identified with Exviera in combination with ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir and ribavirin

Frequency	**Exviera and ombitasvir/paritaprevir/ritonavir + ribavirin* N = 2,044**	**Exviera and ombitasvir/paritaprevir/ritonavir N = 588**
Blood and lymphatic system disorders		
Common	Anaemia	
Psychiatric disorders		
Very common	Insomnia	
Gastrointestinal disorders		
Very common	Nausea	
Skin and subcutaneous tissue disorders		
Very common	Pruritus	
Common		Pruritus
Rare	angioedema	angioedema
General disorders and administration and administration site conditions		
Very common	Asthenia Fatigue	

*Data set includes all genotype 1-infected subjects in Phase 2 and 3 trials including subjects with cirrhosis. Note: For laboratory abnormalities refer to Table 4.

Description of selected adverse reactions

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 trial designs.

Table 4. Selected treatment emergent laboratory abnormalities

Laboratory parameters	SAPPHIRE I and II	PEARL II, III, and IV	TURQUOISE II (subjects with cirrhosis)
	Exviera and ombitasvir/paritaprevir /ritonavir + ribavirin **12 weeks** **N = 770** **n (%)**	**Exviera and ombitasvir/paritaprevir /ritonavir** **12 weeks** **N = 509** **n (%)**	**Exviera and ombitasvir/paritaprevir /ritonavir + ribavirin** **12 or 24 weeks** **N = 380** **n (%)**
ALT			
>5-20 × ULN* (Grade 3)	6/765 (0.8%)	1/509 (0.2%)	4/380 (1.1%)
>20 × ULN (Grade 4)	3/765 (0.4%)	0	2/380 (0.5%)
Haemoglobin			
<100-80 g/L (grade 2)	41/765 (5.4%)	0	30/380 (7.9%)
<80-65 g/L (grade 3)	1/765 (0.1%)	0	3/380 (0.8%)
<65 g/L (Grade 4)	0	0	1/380 (0.3%)
Total bilirubin			
>3-10 × ULN (grade 3)	19/765 (2.5%)	2/509 (0.4%)	37/380 (9.7%)
>10 × ULN (grade 4)	1/765 (0.1%)	0	0
*ULN: Upper Limit of Normal			

Serum ALT elevations

In a pooled analysis of clinical trials with Exviera and ombitasvir/paritaprevir/ritonavir with and without ribavirin, 1% of subjects experienced serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. As the incidence of such elevations was 26% among women taking a concomitant ethinylestradiol-containing medicine, such medicinal products are contraindicated with Exviera and ombitasvir/paritaprevir/ritonavir. No increase in incidence of ALT elevations was observed with other types of systemic estrogens commonly used for hormone replacement therapy (e.g., estradiol and conjugated estrogens). ALT elevations were typically asymptomatic, generally occurred during the first 4 weeks of treatment (mean time 20 days, range 8-57 days) and most resolved with ongoing therapy. Two patients discontinued Exviera and ombitasvir/paritaprevir/ritonavir due to elevated ALT, including one on ethinylestradiol. Three interrupted Exviera and ombitasvir/paritaprevir/ritonavir for one to seven days, including one on ethinylestradiol. The majority of these ALT elevations were transient and assessed as related to Exviera and ombitasvir/paritaprevir/ritonavir. Elevations in ALT were generally not associated with bilirubin elevations. Cirrhosis was not a risk factor for elevated ALT (see section 4.4).

Serum bilirubin elevations

Transient elevations in serum bilirubin (predominantly indirect) were observed in subjects receiving Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin, related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced haemolysis. 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 subjects who did not receive ribavirin.

Liver transplant recipients

The overall safety profile in HCV-infected transplant recipients who were administered Exviera and ombitasvir/paritaprevir/ritonavir and ribavirin (in addition to their immunosuppressant medicinal products) was similar to subjects treated with Exviera and ombitasvir/paritaprevir/ritonavir and ribavirin in phase 3 clinical trials, although some adverse reactions were increased in frequency. 10 subjects

(29.4%) had at least one post baseline haemoglobin value of less than 10 g/dL. 10 of 34 subjects (29.4%) dose modified ribavirin due to decrease in haemoglobin and 2.9% (1/34) had an interruption of ribavirin. Ribavirin dose modification did not impact SVR rates. 5 subjects required erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No subject received a blood transfusion.

HIV/HCV co-infected patients

The overall safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. Transient elevations in total bilirubin >3 x ULN (mostly indirect) occurred in 17 (27.0%) subjects; 15 of these subjects were receiving atazanavir. None of the subjects with hyperbilirubinemia had concomitant elevations of aminotransferases.

Post Marketing Adverse Reactions

The following post marketing adverse reactions have been observed during treatment with Exviera with ombitasvir/paritaprevir/ritonavir with or without ribavirin. The frequency of these events is unknown. The adverse reactions are presented by the System Organ Class.

Immune system disorders: Anaphylactic reactions.

Hepatobiliary disorders: Hepatic decompensation and hepatic failure (see section 4.4).

Paediatric population

The safety of Exviera in children and adolescents aged < 18 years has not yet been established. No data are available.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

The highest documented single dose of dasabuvir administered to healthy volunteers was 2 g. No study drug-related adverse reactions or clinically significant laboratory abnormalities were observed. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; direct-acting antivirals, ATC code: J05AP09

Mechanism of action

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.

Co-administration of dasabuvir with ombitasvir/paritaprevir/ritonavir 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. Refer to the prescribing information of ombitasvir/paritaprevir/ritonavir for its pharmacological properties.

Activity in cell culture and biochemical studies

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).

The M1 metabolite of dasabuvir had EC_{50} values of 39 and 8 nM against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays, respectively, and the activity of the M1 metabolite was attenuated 3- to 4-fold in the presence of 40% human plasma. Dasabuvir had reduced activity in biochemical assays against NS5B polymerases from HCV genotypes 2a, 2b, 3a and 4a (IC_{50} values ranging from 900 nM to >20 μM).

Resistance

In cell culture

Resistance to dasabuvir conferred by variants in NS5B selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterised in the appropriate genotype 1a or 1b replicons.

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 subjects with genotype 1 HCV infection, who were treated with dasabuvir, ombitasvir and paritaprevir with or without ribavirin in Phase 2b and 3 clinical trials, was conducted to explore the association between baseline NS3/4A, NS5A or NS5B substitutions/polymorphisms and treatment outcome in these 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 subjects, the presence of baseline variants appears to have little impact on the likelihood of achieving SVR.

In clinical studies

Of the 2,510 HCV genotype 1 infected subjects who were treated with regimens containing dasabuvir, ombitasvir and paritaprevir with or without ribavirin (for 8, 12 or 24 weeks) in Phase 2b and 3 clinical trials, a total of 74 subjects (3%) experienced virologic failure (primarily post-treatment relapse). Treatment-emergent variants and their prevalence in these virologic failure populations are shown in Table 5. In the 67 genotype 1a infected subjects, NS3 variants were observed in 50 subjects, NS5A variants were observed in 46 subjects, NS5B variants were observed in 37 subjects, and treatment-emergent variants were seen in all 3 drug targets in 30 subjects. In the 7 genotype 1b infected subjects, treatment-emergent variants were observed in NS3 in 4 subjects, in NS5A in 2 subjects, and in both NS3 and NS5A in 1 subject. No genotype 1b infected subjects had treatment-emergent variants in all 3 drug targets.

Table 5. Treatment-emergent amino acid substitutions in the pooled analysis of Exviera and ombitasvir/paritaprevir/ritonavir, with and without RBV 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 subjects 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 subjects.
e. Observed in combination in 6% (4/67) of the subjects.

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 dasabuvir, ombitasvir and paritaprevir resistance-associated amino acid substitutions in NS5B, NS5A and NS3, respectively, was assessed in genotype 1a-infected subjects in Phase 2b trials. Dasabuvir treatment-emergent variants M414T, G554S, S556G, G558R or D559G/N in NS5B were observed in 34 subjects. Ombitasvir treatment-emergent variants M28T, M28V or Q30R in NS5A were observed in 32 subjects. Paritaprevir treatment-emergent variants V36A/M, R155K or D168V were observed in NS3 in 47 subjects.

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 Exviera and ombitasvir/paritaprevir/ritonavir -resistance-associated substitutions on future treatment 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 dasabuvir, ombitasvir, or paritaprevir treatment experience on the efficacy of other NS5A inhibitors, NS3/4A protease inhibitors, or NS5B inhibitors has not been studied.

Clinical efficacy and safety

The efficacy and safety of Exviera in combination with ombitasvir/paritaprevir/ritonavir with and without ribavirin was evaluated in eight Phase 3 clinical trials, including two trials exclusively in subjects with compensated cirrhosis (Child-Pugh A), in over 2,360 subjects with genotype 1 chronic hepatitis C infection as summarised in Table 6.

Table 6. Phase 3 global multicentre trials conducted with Exviera and ombitasvir/paritaprevir/ritonavir with or without ribavirin (RBV).

Trial	Number of subjects treated	HCV genotype (GT)	Summary of study design
Treatment-naïve, without cirrhosis			
SAPPHIRE I	631	GT1	Arm A: Exviera and ombitasvir/paritaprevir/ritonavir + RBV Arm B: Placebo
PEARL III	419	GT1b	Arm A: Exviera and ombitasvir/paritaprevir/ritonavir + RBV Arm B: Exviera and ombitasvir/paritaprevir/ritonavir
PEARL IV	305	GT1a	Arm A: Exviera and ombitasvir/paritaprevir/ritonavir + RBV Arm B: Exviera and ombitasvir/paritaprevir/ritonavir
GARNET (open-label)	166	GT1b	Exviera and ombitasvir/paritaprevir/ritonavir (8 weeks)
Peginteferon+ribavirin-experienced, without cirrhosis			
SAPPHIRE II	394	GT1	Arm A: Exviera and ombitasvir/paritaprevir/ritonavir + RBV Arm B: Placebo
PEARL II (open-label)	179	GT1b	Arm A: Exviera and ombitasvir/paritaprevir/ritonavir + RBV Arm B: Exviera and ombitasvir/paritaprevir/ritonavir
Treatment-naïve and peginterferon+ribavirin-experienced, with compensated cirrhosis			
TURQUOISE II (open-label)	380	GT1	Arm A: Exviera and ombitasvir/paritaprevir/ritonavir + RBV (12 weeks) Arm B: Exviera and

			ombitasvir/paritaprevir/ritonavir + RBV (24 weeks)
TURQUOISE III (open-label)	60	GT1b	Exviera and ombitasvir/paritaprevir/ritonavir (12 weeks)

In all eight trials, the Exviera dose was 250 mg twice daily and the ombitasvir/paritaprevir/ritonavir dose was 25 mg/150 mg/100 mg once daily. For subjects who received ribavirin, the ribavirin dose was 1000 mg per day for subjects weighing less than 75 kg or 1200 mg per day for subjects weighing greater than or equal to 75 kg.

Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate in the Phase 3 studies and was defined as unquantifiable or undetectable HCV RNA 12 weeks after the end of treatment (SVR12). Treatment duration was fixed in each trial and was not guided by subjects' 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 (except GARNET which used COBAS AmpliPrep/COBAS TaqMan HCV Test v2.0). The High Pure system assay had a lower limit of quantification (LLOQ) of 25 IU per mL and the AmpliPrep assay had a LLOQ of 15 IU per mL.

Clinical trials in treatment-naïve adults

SAPPHIRE-I – genotype 1, treatment-naïve

SAPPHIRE-I was a randomised, global multicentre, double-blind, placebo-controlled trial conducted in 631 treatment-naïve adults with genotype 1 chronic hepatitis C virus infection without cirrhosis. Exviera and ombitasvir/paritaprevir/ritonavir were given for 12 weeks of treatment in combination with ribavirin. Subjects randomised to the placebo arm received placebo for 12 weeks, after which they received open-label Exviera and ombitasvir/paritaprevir/ritonavir in combination with ribavirin for 12 weeks.

Treated subjects (N=631) had a median age of 52 years (range: 18 to 70); 54.5% were male; 5.4% were Black; 16.2% had a body mass index of at least 30 kg/m^2; 15.2% had a history of depression or bipolar disorder; 69.3% had IL28B non-CC genotype; 79.1% had baseline HCV RNA levels of at least 800,000 IU/mL; 15.4% had portal fibrosis (F2) and 8.7% had bridging fibrosis (F3); 67.7% had HCV genotype 1a infection; 32.3% had HCV genotype 1b infection.

Table 7 shows the SVR12 rates for genotype 1-infected, treatment-naïve subjects receiving Exviera and ombitasvir/paritaprevir/ritonavir in combination with ribavirin for 12 weeks in SAPPHIRE-I.

Table 7. SVR12 for genotype 1-infected treatment-naïve subjects in SAPPHIRE-I

Treatment outcome	**Exviera and ombitasvir/paritaprevir/ritonavir with RBV for 12 weeks**		
	n/N	**%**	**95% CI**
Overall SVR12	456/473	96.4	94.7, 98.1
HCV genotype 1a	308/322	95.7	93.4, 97.9
HCV genotype 1b	148/151	98.0	95.8, 100.0
Outcome for subjects without SVR12			
On-treatment VF[a]	1/473	0.2	
Relapse	7/463	1.5	
Other[b]	9/473	1.9	

a. 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. Other includes early drug discontinuation not due to virologic failure and missing HCV RNA values in the SVR12 window.

No subjects with HCV genotype 1b infection experienced on-treatment virologic failure and one subject with HCV genotype 1b infection experienced relapse.

PEARL-III – genotype 1b, treatment-naïve

PEARL-III was a randomised, global multicentre, double-blind, controlled trial conducted in 419 treatment-naïve adults with genotype 1b chronic hepatitis C virus infection without cirrhosis. Subjects were randomised in a 1:1 ratio to receive Exviera and ombitasvir/paritaprevir/ritonavir with or without ribavirin for 12 weeks of treatment.

Treated subjects (N=419) had a median age of 50 years (range: 19 to 70); 45.8% were male; 4.8% were Black; 16.5% had a body mass index of at least 30 kg/m^2; 9.3% had a history of depression or bipolar disorder; 79.0% had IL28B non-CC genotype; 73.3% had baseline HCV RNA of at least 800,000 IU/mL; 20.3% had portal fibrosis (F2) and 10.0% had bridging fibrosis (F3).

Table 8 shows the SVR12 rates for genotype 1b-infected, treatment-naïve subjects who received Exviera and ombitasvir/paritaprevir/ritonavir with or without ribavirin for 12 weeks in PEARL III. In this study, Exviera and ombitasvir/paritaprevir/ritonavir without ribavirin had similar SVR12 rates (100%) compared to Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin (99.5%).

Table 8. SVR12 for genotype 1b-infected treatment-naïve subjects in PEARL III

Treatment outcome	Exviera and ombitasvir/paritaprevir/ritonavir for 12 weeks					
	With RBV			Without RBV		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	209/210	99.5	98.6, 100.0	209/209	100	98.2, 100.0
Outcome for subjects without SVR12						
On-treatment VF	1/210	0.5		0/209	0	
Relapse	0/210	0		0/209	0	
Other	0/210	0		0/209	0	

PEARL-IV– genotype 1a, treatment-naïve

PEARL-IV was a randomised, global multicentre, double-blind, controlled trial conducted in 305 treatment-naïve adults with genotype 1a chronic hepatitis C virus infection without cirrhosis. Subjects were randomised in a 1:2 ratio to receive Exviera and ombitasvir/paritaprevir/ritonavir with or without ribavirin for 12 weeks of treatment.

Treated subjects (N=305) had a median age of 54 years (range: 19 to 70); 65.2% were male; 11.8% were Black; 19.7% had a body mass index of at least 30 kg/m^2; 20.7% had a history of depression or bipolar disorder; 69.2% had IL28B non-CC genotype; 86.6% had baseline HCV RNA levels of at least 800,000 IU/mL; 18.4% had portal fibrosis (F2) and 17.7% had bridging fibrosis (F3).

Table 9 shows the SVR12 rates for genotype 1a-infected, treatment-naïve subjects who received Exviera and ombitasvir/paritaprevir/ritonavir with or without ribavirin for 12 weeks in PEARL IV. Exviera and ombitasvir/paritaprevir/ritonavir without ribavirin was not non-inferior to Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin.

Table 9. SVR12 for genotype 1a-infected treatment-naïve subjects in PEARL IV

Treatment outcome	Exviera and ombitasvir/paritaprevir/ritonavir for 12 weeks					
	With RBV			Without RBV		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	97/100	97.0	93.7, 100.0	185/205	90.2	86.2, 94.3
Outcome for subjects without SVR12						
On-treatment VF	1/100	1.0		6/205	2.9	
Relapse	1/98	1.0		10/194	5.2	
Other	1/100	1.0		4/205	2.0	

GARNET – Genotype 1b, Treatment-Naïve without cirrhosis.

Design: open-label, single-arm, global multicentre
Treatment: Exviera and ombitasvir/paritaprevir/ritonavir for 8 weeks

Treated subjects (N=166) had a median age of 53 years (range: 22 to 82); 56.6% were female; 3.0% were Asian; 0.6% were Black; 14.5% had a body mass index of at least 30 kg per m2; 68.5% had IL28B non-CC genotype; 7.2% had baseline HCV RNA levels of at least 6,000,000 IU per mL; 9% had advanced fibrosis (F3) and 98.2% had HCV genotype 1b infection (one subject each had genotype 1a, 1d, and 6 infection).

Table 10. SVR12 for Genotype 1b-infected treatment-naïve subjects without cirrhosis

	Exviera and ombitasvir/paritaprevir/ritonavir for 8 weeks n/N (%)
SVR12	*160/163 (98.2)*
95% CI[a]	*96.1, 100.0*
F0-F1	*138/139 (99.3)*[b]
F2	*9/9 (100)*
F3	*13/15 (86.7)*[c]

a. *Calculated using the normal approximation to the binomial distribution*
b. *1 patient discontinued due to non-compliance*
c. *Relapse in 2/15 patients (confirmed HCV RNA ≥ 15 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA < 15 IU/mL at last observation with at least 51 days of treatment).*

Clinical trials in peginterferon+ribavirin-experienced adults

SAPPHIRE-II – genotype 1, peginterferon+ribavirin-experienced

SAPPHIRE-II was a randomised, global multicentre, double-blind, placebo-controlled trial conducted in 394 subjects with genotype 1 chronic hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment with pegIFN/RBV. Exviera and ombitasvir/paritaprevir/ritonavir in combination with ribavirin was given for 12 weeks of treatment. Subjects randomised to the placebo arm received placebo for 12 weeks, after which they received Exviera and ombitasvir/paritaprevir/ritonavir in combination with ribavirin for 12 weeks.

Treated subjects (N=394) had a median age of 54 years (range: 19 to 71); 49.0% were prior pegIFN/RBV null responders; 21.8/% were prior pegIFN/RBV partial responders; and 29.2% were prior pegIFN/RBV

relapsers; 57.6% were male; 8.1% were Black; 19.8% had a body mass index of at least 30 kg/m^2; 20.6% had a history of depression or bipolar disorder; 89.6% had IL28B non-CC genotype; 87.1% had baseline HCV RNA levels of at least 800,000 IU per mL; 17.8% had portal fibrosis (F2) and 14.5% had bridging fibrosis (F3); 58.4% had HCV genotype 1a infection; 41.4% had HCV genotype 1b infection.

Table 11 shows the SVR12 rates for treatment-experienced subjects with genotype 1-infection receiving Exviera and ombitasvir/paritaprevir/ritonavir in combination with ribavirin for 12 weeks in SAPPHIRE-II.

Table 11. SVR12 for genotype 1-infected peginterferon+ribavirin-experienced subjects in SAPPHIRE-II

	Exviera and ombitasvir/paritaprevir/ritonavir with RBV for 12 weeks		
Treatment outcome	**n/N**	**%**	**95% CI**
Overall SVR12	286/297	96.3	94.1, 98.4
HCV genotype 1a	166/173	96.0	93.0, 98.9
Prior pegIFN/RBV null responder	83/87	95.4	91.0, 99.8
Prior pegIFN/RBV partial responder	36/36	100	100.0, 100.0
Prior pegIFN/RBV relapser	47/50	94.0	87.4, 100.0
HCV genotype 1b	119/123	96.7	93.6, 99.9
Prior pegIFN/RBV null responder	56/59	94.9	89.3, 100.0
Prior pegIFN/RBV partial responder	28/28	100	100.0, 100.0
Prior pegIFN/RBV relapser	35/36	97.2	91.9, 100.0
Outcome for subjects without SVR12			
On-treatment VF	0/297	0	
Relapse	7/293	2.4	
Other	4/297	1.3	

No subjects with HCV genotype 1b infection experienced on-treatment virologic failure and 2 subjects with HCV genotype 1b infection experienced relapse.

PEARL-II – genotype 1b, peginterferon+ribavirin-experienced

PEARL-II was a randomised, global multicentre, 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. Subjects were randomised in a 1:1 ratio to receive Exviera and ombitasvir/paritaprevir/ritonavir with or without ribavirin for 12 weeks of treatment.

Treated subjects (N=179) had a median age of 57 years (range: 26 to 70); 35.2% were prior pegIFN/RBV null responders; 28.5% were prior pegIFN/RBV partial responders; and 36.3% were prior pegIFN/RBV relapsers; 54.2% were male; 3.9% were Black; 21.8% had a body mass index of at least 30 kg/m^2; 12.8% had a history of depression or bipolar disorder; 90.5% had IL28B non-CC genotype; 87.7% had baseline HCV RNA levels of at least 800,000 IU/mL; 17.9% had portal fibrosis (F2) and 14.0% had bridging fibrosis (F3).

Table 12 shows the SVR12 rates for genotype 1b-infected, treatment-experienced subjects who received Exviera and ombitasvir/paritaprevir/ritonavir with or without ribavirin for 12 weeks in PEARL II. In this study, Exviera and ombitasvir/paritaprevir/ritonavir without ribavirin had a similar SVR12 rate (100%) compared to Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin (97.7%).

Table 12. SVR12 for genotype 1b-infected peginterferon+ribavirin-experienced subjects in PEARL II

Treatment outcome	Exviera and ombitasvir/paritaprevir/ritonavir for 12 weeks					
	With RBV			Without RBV		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	86/88	97.7	94.6, 100.0	91/91	100	95.9, 100.0
Prior pegIFN/RBV null responder	30/31	96.8	90.6, 100.0	32/32	100	89.3, 100.0
Prior pegIFN/RBV partial responder	24/25	96.0	88.3, 100.0	26/26	100	87.1, 100.0
Prior pegIFN/RBV relapser	32/32	100	89.3, 100.0	33/33	100	89.6, 100.0
Outcome for subjects without SVR12						
On-treatment VF	0/88	0		0/91	0	
Relapse	0/88	0		0/91	0	
Other	2/88	2.3		0/91	0	

Clinical trial in subjects with compensated cirrhosis

TURQUOISE-II– genotype 1, treatment-naïve or peginterferon+ribavirin-experienced subjects with compensated cirrhosis

TURQUOISE-II was a randomised, global multicentre, open-label trial conducted exclusively in 380 genotype 1-infected subjects with compensated cirrhosis (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Exviera and ombitasvir/paritaprevir/ritonavir in combination with ribavirin were administered for either 12 or 24 weeks of treatment.

Treated subjects (N=380) had a median age of 58 years (range: 21 to 71); 42.1% were treatment-naïve, 36.1% were prior pegIFN/RBV null responders; 8.2% were prior pegIFN/RBV partial responders, 13.7% were prior pegIFN/RBV relapsers; 70.3% were male; 3.2% were Black; 28.4% had a body mass index of at least 30 kg/m^2; 14.7% had platelet counts of less than 90 x 10^9/L; 49.7% had albumin less than 40 g/L; 86.1% had baseline HCV RNA levels of at least 800,000 IU/mL; 81.8% had IL28B non-CC genotype; 24.7% had a history of depression or bipolar disorder; 68.7% had HCV genotype 1a infection, 31.3% had HCV genotype 1b infection.

Table 13 shows the SVR12 rates for genotype 1-infected subjects with compensated cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

Table 13. SVR12 for genotype 1-infected subjects with compensated cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV

Treatment outcome	Exviera and ombitasvir/paritaprevir/ritonavir with RBV					
	12 weeks			24 weeks		
	n/N	%	CI[a]	n/N	%	CI[a]
Overall SVR12	191/208	91.8	87.6, 96.1	166/172	96.5	93.4, 99.6
HCV genotype 1a	124/140	88.6	83.3, 93.8	115/121	95.0	91.2, 98.9
Treatment naïve	59/64	92.2		53/56	94.6	
Prior pegIFN/RBV null responders	40/50	80.0		39/42	92.9	
Prior pegIFN/RBV partial responders	11/11	100		10/10	100	
Prior pegIFN/RBV Prior relapsers	14/15	93.3		13/13	100	
HCV genotype 1b	67/68	98.5	95.7, 100	51/51	100	93.0, 100
Treatment naïve	22/22	100		18/18	100	
Prior pegIFN/RBV null responders	25/25	100		20/20	100	
Prior pegIFN/RBV partial responders	6/7	85.7		3/3	100	
Prior pegIFN/RBV Prior relapsers	14/14	100		10/10	100	
Outcome for subjects without SVR12						
On-treatment VF	1/208	0.5		3/172	1.7	
Relapse	12/203	5.9		1/164	0.6	
Other	4/208	1.9		2/172	1.21	

a. 97.5% confidence intervals are used for the primary efficacy endpoints (overall SVR12 rate); 95% confidence intervals are used for additional efficacy endpoints (SVR12 rates in HCV genotype 1a and 1b-infected subjects).

Relapse rates in GT1a cirrhotic subjects by baseline laboratory values are presented in Table 14.

Table 14. TURQUOISE-II: relapse rates by baseline laboratory values after 12 and 24 weeks of treatment in subjects with genotype 1a infection and compensated cirrhosis

	Exviera and ombitasvir/paritaprevir/ritonavir with RBV 12-week arm	**Exviera and ombitasvir/paritaprevir/ritonavir with RBV 24-week arm**
Number of Responders at the End of Treatment	135	113
AFP* < 20 ng/mL, platelets ≥ 90 x 10^9/L, AND albumin ≥ 35 g/L prior to treatment		
Yes (for all three parameters listed above)	1/87 (1%)	0/68 (0%)
No (for any parameter listed above)	10/48 (21%)	1/45 (2%)
*AFP= serum alpha fetoprotein		

In subjects with all three favourable baseline laboratory values (AFP < 20 ng/mL, platelets ≥ 90 x 10^9/L, and albumin ≥ 35 g/L), relapse rates were similar in subjects treated for 12 or 24 weeks.

TURQUOISE-III: Clinical Trial of GT1b-Infected Subjects with Cirrhosis without RBV

TURQUOISE-III is a Phase 3b, open-label, single-arm, multicentre study evaluating the efficacy and safety of Exviera and ombitasvir/paritaprevir/ritonavir (without ribavirin) administered for 12 weeks in HCV GT1b-infected, treatment-naïve and pegIFN/RBV treatment-experienced adults with compensated cirrhosis.
60 patients were randomized and treated, and 60/60 (100%) achieved SVR12. Main characteristics are shown below.

Table 15. Main demographics in TURQUOISE-III

Characteristics	**N = 60**
Age, median (range) years	60.5 (26-78)
Male gender, n (%)	37 (61)
IL28B Non-CC genotype, n (%)	50 (83)
Prior HCV Treatment:	
naïve, n (%)	27 (45)
Peg-IFN + RBV, n (%)	33 (55)
Baseline albumin, median g/L	40.0
< 35, n (%)	10 (17)
≥ 35, n (%)	50 (83)
Baseline platelet count, median ($\times 10^9$/L)	132.0
< 90, n (%)	13 (22)
≥ 90, n (%)	47 (78)

Pooled analyses of clinical trials

Durability of response

Overall, 660 subjects in Phase 2 and 3 clinical trials had HCV RNA results for both the SVR12 and SVR24 time points. Among these subjects, the positive predictive value of SVR12 on SVR24 was 99.8%.

Pooled efficacy analysis

In Phase 3 clinical trials, 1075 subjects (including 181 with compensated cirrhosis) received the recommended regimen (see section 4.2). Table 16 shows SVR rates for these subjects.

In subjects who received the recommended regimen, 97% achieved SVR overall (among which 181 subjects with compensated cirrhosis achieved 97% SVR), while 0.5% experienced virologic breakthrough and 1.2% experienced post-treatment relapse.

Table 16. SVR12 rates for recommended treatment regimens by patient population

	HCV Genotype 1b Exviera and ombitasvir/paritaprevir/ritonavir		HCV Genotype 1a Exviera and ombitasvir/paritaprevir/ritonavir with RBV	
	Without cirrhosis	**With compensated cirrhosis**	**Without cirrhosis**	**With compensated cirrhosis**
Treatment duration	**12 weeks**	**12 weeks**	**12 weeks**	**24 weeks**
Treatment-naïve	100% (210/210)	100% (27/27)	96% (403/420)	95% (53/56)
pegIFN + RBV-experienced	100% (91/91)	100% (33/33)	96% (166/173)	95% (62/65)
Prior relapse	100% (33/33)	100% (3/3)	94% (47/50)	100% (13/13)
Prior partial response	100% (26/26)	100% (5/5)	100% (36/36)	100% (10/10)
Prior null response	100% (32/32)	100% (7/7)	95% (83/87)	93% (39/42)
Other pegIFN/RBV failures	0	100% (18/18)[+]	0	0
TOTAL	100% (301/301)	100% (60/60)	96% (569/593)	95% (115/121)

+ 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 subjects did not require ribavirin dose adjustments during therapy. In the 8.5% of subjects who had ribavirin dose adjustments during therapy, the SVR rate (98.5%) was comparable to subjects who maintained their starting ribavirin dose throughout treatment.

Clinical Trial in subjects with HCV genotype 1 Infection/HIV-1 co-infection

In an open-label clinical trial (TURQUOISE-I) the safety and efficacy of 12 or 24 weeks of treatment with Exviera and ombitasvir/paritaprevir/ritonavir and ribavirin was evaluated in 63 subjects with genotype 1 chronic hepatitis C co-infected with HIV-1. See section 4.2 for dosing recommendations in HCV/HIV-1 co-infected patients. Subjects 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 subjects (N = 63) had a median age of 51 years (range: 31 to 69); 24% of subjects were Black; 81% of subjects had IL28B non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection.

Table 17 shows the SVR12 rates for subjects with HCV genotype 1 infection and HIV-1 co-infection in TURQUOISE-I.

Table 17. SVR12 for HIV-1 co-infected Subjects in TURQUOISE-I

Endpoint	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 for subjects not achieving SVR12		
On-treatment virologic failure	0	1
Post-treatment relapse	1	2[a]
Other	1	0

a. These virologic failures appear to have resulted from reinfection based on analyses of baseline and virologic failure samples

In TURQUOISE-I, the SVR12 rates in HCV/HIV-1 co-infected subjects were consistent with SVR12 rates in the phase 3 trials of HCV mono-infected subjects. 7 of 7 subjects with genotype 1b infection and 51 of 56 subjects with genotype 1a infection achieved SVR12. 5 of 6 subjects with compensated cirrhosis in each arm achieved SVR12.

Clinical Trial in liver transplant recipients

In the CORAL-1 study, the safety and efficacy of Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin for 24 weeks was studied in 34 HCV genotype 1-infected liver transplant recipients who were at least 12 months post-transplant at study enrolment. The dose of ribavirin was individualized at the discretion of the investigator, with most patients receiving 600 to 800 mg as a starting dose, and most patients also receiving 600 to 800 mg per day at the end of treatment.

34 subjects (29 with HCV genotype 1a infection and 5 with HCV genotype 1b infection) were enrolled who had not received treatment for HCV infection after transplantation and had a METAVIR fibrosis score of F2 or less. 33 out of the 34 subjects (97.1%) achieved SVR12 (96.6% in subjects with genotype 1a infection and 100% in subjects with genotype 1b infection). One subject with HCV genotype 1a infection relapsed post-treatment.

Clinical Trial in patients receiving chronic opioid substitution therapy

In a phase 2, multicentre, open-label, single arm study, 38 treatment-naïve or pegIFN/RBV treatment experienced, non-cirrhotic subjects with genotype 1 infection who were on stable doses of methadone (N=19) or buprenorphine with or without naloxone (N=19) received 12 weeks of Exviera in combination with ombitasvir/paritaprevir/ritonavir and ribavirin. Treated subjects had a median age of 51 years (range: 26 to 64); 65.8% were male and 5.3% were Black. A majority (86.8%) had baseline HCV RNA levels of at least 800,000 IU/mL and a majority (84.2%) had genotype 1a infection; 68.4% had IL28B non-CC genotype; 15.8% had portal fibrosis (F2) and 5.3% had bridging fibrosis (F3); and 94.7% were naïve to prior HCV treatment.

Overall, 37 (97.4%) of 38 subjects achieved SVR12. No subjects experienced on-treatment virologic failure or relapse.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of the combination of Exviera with ombitasvir/paritaprevir/ritonavir have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Table 18 shows mean C_{max} and AUC of Exviera 250 mg twice daily with ombitasvir/paritaprevir/ritonavir 25 mg/150 mg/100 mg once daily following multiple doses with food in healthy volunteers.

Table 18. Geometric mean C_{max}, AUC of multiple doses of Exviera 250 mg twice daily and ombitasvir/paritaprevir/ritonavir 25 mg/150 mg/100 mg once daily with food in healthy volunteers

	C_{max} (ng/ml) (CV%)	**AUC (ng*hr/ml) (CV%)**
Dasabuvir	1030 (31)	6840 (32)

Absorption

Dasabuvir was absorbed after oral administration with mean T_{max} of approximately 4 to 5 hours. Dasabuvir exposures increased in a dose proportional manner and accumulation is minimal. Pharmacokinetic steady state for dasabuvir when coadministered with ombitasvir/paritaprevir/ritonavir is achieved after approximately 12 days of dosing.

Effects of food

Dasabuvir should be administered with food. All clinical trials with dasabuvir have been conducted following administration with food.

Food increased the exposure (AUC) of dasabuvir by up to 30% 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 maximise absorption, Exviera should be taken with food without regard to fat or calorie content.

Distribution

Dasabuvir is 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 human ranged from 0.5 to 0.7 indicating that dasabuvir was preferentially distributed in the plasma compartment of whole blood. Dasabuvir was greater than 99.5%, and M1 major metabolite of dasabuvir was 94.5% bound to human plasma proteins over a concentration range of 0.05 to 5 □g/mL. At steady-state the exposures ratio of M1 to dasabuvir is approximately 0.6. Taking into account the protein binding and *in vitro* activity of M1 against HCV genotype 1, its contribution to efficacy is expected to be similar to that of dasabuvir. In addition, M1 is a substrate of the hepatic uptake transporters OATP family and OCT1 and thus, the hepatocyte concentration and thereby contribution to efficacy, may be larger than dasabuvir.

Biotransformation

Dasabuvir is predominantly metabolised 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 following single dose; it's formed via oxidative metabolism predominantly by CYP2C8.

Elimination

Following dosing of dasabuvir with ombitasvir/ paritaprevir /ritonavir, mean plasma half-life of dasabuvir was approximately 6 hours. Following a 400 mg ^{14}C-dasabuvir dose, approximately 94% of the radioactivity was recovered in faeces with limited radioactivity (approximately 2%) in urine. Unchanged dasabuvir accounted for 26.2% and M1 for 31.5% of the total dose in faeces. M1 is mainly cleared through direct biliary excretion with the contribution of UGT-mediated glucuronidation and, to a small extent, oxidative metabolism.

Dasabuvir does not inhibit organic anion transporter (OAT1) *in vivo* and is not expected to inhibit organic cation transporters (OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations; therefore, Exviera does not affect medicinal product transport by these proteins.

Special populations

Elderly

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, a 10 year increase or decrease in age from 54 years (median age in the Phase 3 studies) would results in <10% change in dasabuvir exposures. There is no pharmacokinetic information in patients >75 years.

Sex or body weight

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, female subjects would have approximately 14 to 30% higher dasabuvir exposures than male subjects. A 10 kg change in body weight from 76 kg (median weight in the Phase 3 studies) would result in <10% change in dasabuvir exposures.

Race or ethnicity

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, Asian subjects had 29% to 39% higher dasabuvir exposures than non-Asian subjects.

Renal impairment

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 150 mg, and ritonavir 100 mg, with dasabuvir 400 mg were evaluated in subjects with mild (CrCl: 60 to 89 ml/min), moderate (CrCl: 30 to 59 ml/min) and severe (CrCl: 15 to 29 ml/min) renal impairment, relative to subjects with normal renal function.

In subjects with mild, moderate and severe renal impairment, dasabuvir mean AUC values were 21% higher, 37% higher and 50% higher, respectively. Dasabuvir M1 AUC values were 6% lower, 10% lower, and 13% lower, respectively.

The changes in dasabuvir exposures in subjects with mild, moderate and severe renal impairment are not considered to be clinically significant. Exviera has not been studied in patients on dialysis (see section 4.2).

Hepatic impairment

Pharmacokinetics of the combination of dasabuvir 400 mg, with ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg were evaluated in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, relative to subjects with normal hepatic function.

In subjects with mild, moderate and severe hepatic impairment, dasabuvir AUC values were 17% higher, 16% lower and 325% higher, respectively. The AUC values of dasabuvir M1 metabolite were unchanged, 57% lower, and 77% higher, respectively. Plasma protein binding of dasabuvir and its M1 metabolite were not meaningfully different in subjects with hepatic impairment compared to normal control subjects (see sections 4.2, 4.4 and 4.8).

Paediatric population

The pharmacokinetics of Exviera with ombitasvir/paritaprevir/ritonavir in paediatric patients has not been investigated (see section 4.2).

5.3 Preclinical safety data

Dasabuvir 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.

Dasabuvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (2 g/kg/day), resulting in dasabuvir AUC exposures approximately 19-fold higher than those in humans at the recommended dose of 500 mg (250 mg twice daily).

Similarly, dasabuvir was not carcinogenic in a 2-year rat study up to the highest dose tested (800 mg/kg/day), resulting in dasabuvir exposures approximately 19-fold higher than those in humans at 500 mg.
Dasabuvir had no effects on embryo-foetal viability or on fertility in rodents and were not teratogenic in two species. No adverse effects on behaviour, reproduction or development of offspring were reported. The highest dasabuvir dose tested produced exposures equal to 16 to 24-fold (rat) or 6-fold (rabbit) the exposures in humans at the maximum recommended clinical dose.

Dasabuvir was the predominant component observed in the milk of lactating rats, without effect on nursing pups. Elimination half-life in rat milk was slightly shorter than in plasma, AUC was about 2 fold of that in plasma. Since dasabuvir is a BCRP substrate, distribution to the milk may change if this transporter is inhibited or induced by co-administration of other medicinal products. Dasabuvir-derived material was minimally transferred through the placenta in pregnant rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Copovidone
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film-coating
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol 3350
Talc
Iron oxide yellow
Iron oxide red
Iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Stored at temperatures below 30°C

6.4 Nature and contents of container

Exviera film-coated tablets are supplied in PVC/PE/PCTFE aluminium foil blister packs.
56 tablets (multipack carton containing 4 inner cartons of 14 tablets each).

6.5 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Manufacturer

AbbVie Ltd, UK

8 Marketing authorization holder

AbbVie Biopharmaceuticals Ltd, 4 Haharash St., Hod Hasharon, Israel

9 Registration number: 153-56-34256

<u>עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו- 1986</u>

התרופה משווקת על פי מרשם רופא בלבד

אקסווירה 250 מ"ג טבליות
טבליות מצופות

כל טבליה מכילה:

dasabuvir (as sodium monohydrate)	דאסאבוויר (כסודיום מונוהידראט)
250 mg	250 מ"ג

לרשימת המרכיבים הבלתי פעילים ראה סעיף 6.

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך שאלות נוספות, פנה אל הרופא או אל הרוקח.
תרופה זו נרשמה לטיפול במחלתך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מחלתם דומה.

התרופה אינה מיועדת לילדים ולמתבגרים מתחת לגיל 18.

שפעול מחדש של דלקת נגיפית B:
לפני תחילת הטיפול באקסווירה, על הרופא שלך לעשות לך בדיקות דם לנוכחות זיהום בנגיף הפטיטיס B. במידה ויש לך או היה לך בעבר זיהום בנגיף ההפטיטיס B, אקסווירה עלול לגרום לשפעול מחדש של דלקת כבד נגיפית B, מצב אשר עלול, במקרים מסוימים, להיות קטלני או לגרום לבעיות כבד חמורות (כגון כשל כבדי). שפעול מחדש של דלקת נגיפות B יכול להתרחש בעת הטיפול או אחרי סיום הטיפול באקסווירה. עלייך להיות במעקב קפדני במידה והנך נמצא בסיכון לשפעול מחדש של דלקת כבד נגיפית B בזמן הטיפול באקסווירה או אחריו.

<u>1. למה מיועדת התרופה?</u>
אקסווירה הינה תרופה אנטי ויראלית הניתנת למבוגרים לטיפול בדלקת כבד נגיפית כרונית מסוג C (הפטיטיס C).
התרופה מכילה את החומר הפעיל dasabuvir.
אקסווירה פועלת על ידי עצירת התרבות הוירוס כמו גם את הדבקתם של תאים חדשים בגוף, ובכך מסלקת את הוירוס ממחזור הדם.
תרופה זו אינה פועלת לבדה. התרופה תמיד ניתנת בשילוב עם תרופה אנטי ויראלית נוספת המכילה ombitasvir/paritaprevir/ritonavir.
ייתכן וחלק מהמטופלים ייטלו גם תרופה אנטי ויראלית נוספת הנקראת ribavirin.
הרופא ינחה אותך אלו מהתרופות הללו יש ליטול עם אקסווירה.
חשוב מאד לקרוא בעיון גם את העלון לצרכן של תרופות אנטי וירליות אחרות אשר הנך נוטל בשילוב עם אקסווירה. במידה ויש לך שאלות בנוגע לתרופות שלך, פנה אל הרופא או אל הרוקח.

קבוצה תרפויטית: מעכב פולימראז לא נוקלאוזידי.

<u>2. לפני שימוש בתרופה</u>
אין להשתמש בתרופה אם:

- אתה רגיש (אלרגי) לחומר הפעיל (dasabuvir) או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה (לרשימת המרכיבים הבלתי פעילים, ראה סעיף 6).

- הנך סובל מבעיות כבד חמורות נוספות מלבד מדלקת כבד נגיפית מסוג C (הפטיטיס C).
- הנך נוטל אחת או יותר מהתרופות הרשומות בטבלה מטה. שילוב תרופות אלו עם אקסווירה ו- ombitasvir/paritaprevir/ritonavir עלול לגרום לתופעות חמורות או מסכנות חיים.
תרופות אלו עלולות להשפיע על פעילות של אקסווירה ו – ombitasvir/paritaprevir/ritonavir, ואקסווירה ו- ombitasvir/paritaprevir/ritonavir עלולות להשפיע על הפעילות של תרופות אלו:

תרופות שאין ליטול בשילוב עם אקסווירה	
שם החומר הפעיל	**מטרת נטילת החומר הפעיל**
קרבמזפין- carbamazepine, פניטואין- phenytoin, פנוברביטל- phenobarbital	לטיפול באפילפסיה
אפאוירנז- efavirenz, אטרוירין- etravirine, נוויראפין- nevirapine	לטיפול בזיהום HIV
אנזאלוטמיד- enzalutamide	לטיפול בסרטן הערמונית
תרופות המכילות אתניל אסטרדיול- ethinylestradiol, כגון: מרבית הגלולות, הטבעות הווגינליות והמדבקות	למניעת הריון ולטיפול הורמונלי חלופי
גמפיברוזיל- gemfibrozil	להורדת כולסטרול ושומנים אחרים בדם
מיטוטאן- Mitotane	לטיפול בגידולים מסוימים של בלוטות יותרת הכליה
ריפאמפיצין- rifampicin	לטיפול בזיהומים חיידקיים
תרופות המכילות את צמח הפרע (היפריקום)- St. john's wort (hypericum perforatum)	תרופה צמחית לטיפול בחרדה ודיכאון קל

אין ליטול אקסווירה אם אחד מהנתונים המצוינים מעלה חל עליך. אם אינך בטוח היוועץ ברופא או ברוקח לפני נטילת אקסווירה.

אזהרות מיוחדות הנוגעות לשימוש בתרופה

לפני הטיפול באקסווירה ספר לרופא אם:

- הנך סובל ממחלת כבד, פרט לדלקת כבד נגיפית כרונית מסוג C (הפטיטיס C).
- הנך סובל או סבלת בעבר מדלקת כבד נגיפית מסוג B (הפטיטיס B), כיוון שעלייך להיות במעקב קפדני.
- הנך נשא של נגיף ה-HIV.
- עברת השתלת כבד.
- אם הנך נוטל אקסווירה עם ombitasvir/paritaprevir/ritonavir, ספר לרופא אם הנך חש בתסמינים הבאים העלולים להיות סימן להחמרה בבעיות בכבד:
  - בחילה, הקאה או אובדן תיאבון
  - הנך מבחין בהצהבה של העור או העיניים
  - שתן כהה מהרגיל, צואה בהירה
  - חולשה ועייפות
  - בלבול
  - הנך מבחין בהתנפחות באזור הבטן

אם אחד מהמצבים המצוינים מעלה חל עליך (או שאינך בטוח), היוועץ ברופא או ברוקח לפני נטילת אקסווירה.

ספר לרופא אם יש לך היסטוריה של דיכאון או מחלות פסיכיאטריות. דיכאון, כולל מחשבות והתנהגויות אובדניות, דווחו במטופלים מסויימים הנוטלים תרופה זו, במיוחד במטופלים עם היסטוריה קודמת של דיכאון או מחלות פסיכיאטריות או במטופלים הנוטלים ריבוירין (ribavirin) עם תרופה זו. אתה או הקרובים לך צריכים להודיע באופן מיידי לרופא בכל שינוי בהתנהגות או במצב הרוח ועל כל מחשבה אובדנית שיכולה להיות לך.

בדיקות דם ומעקב

הרופא יפנה אותך לבדיקות דם לפני הטיפול, בתקופת הטיפול ולאחר סיום הטיפול באקסווירה וזאת על מנת שהרופא יוכל :

- להחליט אלו תרופות אחרות עליך ליטול עם אקסווירה ולאיזה פרק זמן.
- לאשר אם הטיפול יעיל והאם נגיף דלקת הכבד מסוג C אינו קיים אצלך יותר.
- לבדוק את תופעות הלוואי של אקסווירה או של תרופות אנטי ויראליות אחרות, אשר הרופא רשם לך לשימוש משולב עם אקסווירה (למשל: ombitasvir/paritaprevir/ritonavir ו-ribavirin).

ילדים ומתבגרים

אין לתת אקסווירה לילדים ומתבגרים מתחת לגיל 18, מכיוון שהשימוש בתרופה בילדים ומתבגרים טרם נבדק.

אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם, תוספי תזונה ותרופות צמחיות ספר על כך לרופא או לרוקח. יש לספר לרופא לפני שאתה מתחיל לקחת כל תרופה חדשה בזמן נטילת אקסווירה.

ישנן תרופות **האסורות לשימוש** עם אקסווירה (ראה רשימת תרופות מעלה בסעיף "אין להשתמש בתרופה אם").

לפני תחילת הטיפול באקסווירה, **יש לספר לרופא או הרוקח** אם אתה לוקח אחת מן התרופות המצוינות בטבלה מטה. ייתכן והרופא יצטרך לשנות את המינון של תרופות אלו.

שם החומר הפעיל	**מטרת נטילת החומר הפעיל**
אלפראזולאם- alprazolam, דיאזפם- diazepam	לטיפול בחרדה, התקפי פאניקה ובעיות שינה
ציקלוספורין- ciclosporin, אברולימוס – everolimus, סירולימוס -sirolimus, טקרולימוס- tacrolimus	תרופות המדכאות את מערכת החיסון
ציקלובנזפרין- cyclobenzaprine, קריסופרודול- carisoprodol	להתכווצויות שרירים
דאביגאטרן- dabigatran,	לדילול דם
דפראסירוקס- deferasirox	להורדת רמות ברזל בדם
דיגוקסין- digoxin, אמלודיפין- amlodipine	לטיפול בבעיות לב או לחץ דם גבוה
פורוסמיד- furosemide	לטיפול באצירת נוזלים בגוף
הידרוקודון- hydrocodone	לטיפול בכאב

אימטיניב- Imatinib	לטיפול בסוגים מסויימים של סרטן הדם
לבותירוקסין- levothyroxine	לבעיות בבלוטת התריס
דרונוויר/ריטונאוויר- darunavir/ritonavir, אטאזאנוויר/ריטונאוויר- atazanavir/ritonavir, רילפיווירין- rilpivirine	לטיפול בזיהום HIV
אומפרזול- omeprazole, לנסופראזול- lansoprazole, אסאומפרזול- esomeprazole	לטיפול בכיבים בקיבה או בעיות אחרות בקיבה
פלובאסטאטין- fluvastatin, פיטבאסטאטין- pitvastatin, פרבסטאטין- pravastatin, רוזובסטאטין- rosuvastatin	להורדת רמת כולסטרול
מפניטואין- s-mephenytoin	לטיפול באפילפסיה
טריפלונאומיד- teriflunomide	לטיפול בטרשת נפוצה
סולפסלזין- Sulfasalazine	לטיפול במחלת מעי דלקתית או לטיפול בדלקת מפרקים שגרונית
וורפרין warfarin ותרופות דומות אחרות הנקראות אנטגוניסטים לויטמין K - vitamin K antagonists	לדילול דם

* ייתכן והרופא שלך יצטרך להעלות את תדירות בדיקות הדם שלך על מנת לבדוק את יכולת קרישת הדם שלך.

לפני השימוש באקסווירה, ספרי לרופא אם הנך נוטלת תרופות המכילות אסטרוגן למניעת הריון או לכל סיבה אחרת. אנא ראי מטה בסעיף "שימוש באמצעים למניעת הריון".

אם אחד מהמצבים המוזכרים מעלה חל עליך (או שאינך בטוח), היוועץ ברופא או ברוקח לפני נטילת אקסווירה.

שימוש בתרופה ומזון
יש ליטול את התרופה עם מזון. אין חשיבות לסוג המזון.

הריון ואמצעים למניעת הריון
השפעת נטילת אקסווירה במהלך ההיריון אינה ידועה. אין להשתמש באקסווירה במהלך הריון, ואין לתת אותה לנשים העלולות להיכנס להיריון ואשר אינן משתמשות באמצעי מניעה יעילים.

- עליך או על בן זוגך/בת זוגתך להשתמש באמצעי מניעה יעילים במהלך הטיפול בתרופה. תכשירים למניעת הריון המכילים אתינילאסטרדיול ethinylestraidol אסורים לשימוש בשילוב עם אקסווירה. שאל את הרופא המטפל שלך על אמצעי המניעה הטובים ביותר עבורך.

  יש לנקוט בזהירות רבה יותר כאשר נוטלים אקסווירה יחד עם ריבוירין ribavirin. ריבוירין Ribavirin עלול לגרום למומים מולדים חמורים. ריבוירין Ribavirin נשאר זמן רב במערכות הגוף, גם לאחר הפסקת הטיפול, לכן אמצעי מניעה יעילים נדרשים במהלך הטיפול וזמן מה לאחריו.

- קיים סיכון למומים מולדים כאשר ריבוירין ribavirin ניתן למטופלת שהרתה.

- קיים גם סיכון למומים מולדים אם ריבוירין ribavirin ניתן למטופל שבת זוגתו הרתה.
- קרא בעיון רב את הסעיף המתייחס ל"אמצעים למניעת הריון" בעלון של ריבוירין ribavirin. חשוב שגם גברים וגם נשים יקראו מידע זה.
- אם הרית או בת זוגתך הרתה במהלך הטיפול באקסווירה עם ribavirin או מספר חודשים לאחר הטיפול, יש לפנות לרופא מיד.

הנקה
אין להניק במהלך הטיפול באקסווירה. לא ידוע אם החומר הפעיל של אקסווירה (dasabuvir) מופרש לחלב אם.

נהיגה ושימוש במכונות
ישנם מטופלים אשר דיווחו על עייפות רבה בעת שימוש באקסווירה עם תרופות אחרות לטיפול דלקת כבד נגיפית מסוג C (הפטיטיס C). אם הנך חש בעייפות, אל תנהג או תשתמש בכלים או מכונות.

מידע חשוב על חלק מהמרכיבים של התרופה
התרופה מכילה לקטוז. במידה שנאמר לך ע"י רופא שיש לך אי סבילות לסוכרים מסויימים, יש להיוועץ ברופא לפני נטילת תרופה זו.

3 . כיצד תשתמש בתרופה?

יש להשתמש בתכשיר תמיד בהתאם להוראות הרופא.
עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן הטיפול בתכשיר.
אקסווירה אינה ניתנת כטיפול יחיד, אלא תמיד בשילוב עם תרופה אנטי וירלית נוספת כמו ombitasvir/paritaprevir/ritonavir. ייתכן והרופא יתן לך תרופה נוספת אנטי וירלית הנקראת ribavirin.

המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.
המינון המקובל הוא: טבליה אחת, פעמיים ביום. יש ליטול טבליה אחת בבוקר ואחת בערב. **אין לעבור על המנה המומלצת**.
צורת הנטילה: יש ליטול את התרופה עם מזון. אין חשיבות לסוג המזון.
יש לבלוע את הטבליות בשלמותן.
אסור לכתוש, לשבור או ללעוס את הטבליות, כיוון שעלול להיות להם טעם מר.
משך הטיפול: 8, 12 או 24 שבועות. הרופא יקבע את משך הטיפול בתרופה.

יש להתמיד בטיפול כפי שהומלץ על ידי הרופא.
גם אם חל שיפור במצב בריאותך, אין להפסיק הטיפול בתרופה אלא אם הרופא הורה לך על כך.
חשוב להשלים את הטיפול במלואו, כך יש את מירב הסיכוי שהתרופות יטפלו בדלקת הכבד הנגיפית מסוג C (הפטיטיס C).

בדיקות ומעקב
הרופא יפנה אותך לבדיקות דם לפני הטיפול, בתקופת הטיפול ולאחר סיום הטיפול באקסווירה (ראה סעיף "אזהרות מיוחדות הנוגעות לשימוש בתרופה").

אם נטלת בטעות מינון גבוה יותר
אם נטלת מנת יתר או אם בטעות בלע ילד מן התרופה, פנה מיד לרופא או לחדר מיון של בית חולים והבא אריזת התרופה איתך.

אם שכחת ליטול את התרופה
חשוב לשים לב ולא לשכוח לקחת את התרופה במועדה.
אם שכחת ליטול תרופה זו בזמן הדרוש:

- **ונותרו יותר מ- 6 שעות** עד למועד נטילת המנה הבאה – יש ליטול את המנה שנשכחה במהירות האפשרית עם מזון.
- **ונותרו פחות מ-6 שעות** עד למועד נטילת המנה הבאה – אין ליטול את המנה שנשכחה, אלא ליטול את המנה הבאה בזמן הרגיל עם מזון.

אין ליטול מנה כפולה כדי לפצות על המנה שנשכחה.

אין ליטול תרופות בחושך! בדוק התווית והמנה <u>בכל פעם</u> שהנך נוטל תרופה. הרכב משקפיים אם הנך זקוק להם.
אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.

<u>4. תופעות לוואי</u>

כמו בכל תרופה, השימוש באקסווירה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן ולא תסבול מאף אחת מהן.

<u>יש להפסיק את השימוש באקסווירה ולפנות מיד לרופא או לעזרה רפואית אם מתקיים אחד מהדברים הבאים:</u>

תופעות לוואי בעת נטילה משולבת של אקסווירה ו-ombitasvir/paritaprevir/ritonavir עם או בלי ribavirin:
תופעות לוואי ששכיחותן אינה ידועה (לא ניתן להעריך על פי המידע הקיים):

- תגובות אלרגיות חמורות, סימנים עלולים לכלול:
  - קשיי נשימה או בליעה
  - סחרחורת, שעלולה להיגרם בעקבות לחץ דם נמוך
  - נפיחות של הפנים, שפתיים, לשון או גרון
  - פריחה או גירוד של העור

<u>ספר לרופא או לרוקח אם אתה מבחין באחת מתופעות הלוואי הבאות:</u>

תופעות לוואי בעת נטילה משולבת של אקסווירה ו-ombitasvir/paritaprevir/ritonavir :
תופעות לוואי שכיחות (תופעות שמופיעות ב–עד משתמש אחד מתוך עשרה):

- גרד

תופעות לוואי נדירות (תופעות שמופיעות בעד משתמש אחד מתוך 1,000):

- התנפחות של שכבות בעור אשר יכולה להשפיע על כל חלק בגוף, כולל הפנים, הלשון או הגרון, ועלולה להוביל לקשיים בבליעה או בנשימה (בצקת מקומית-אנגיואדמה).

תופעות לוואי בעת נטילה משולבת של אקסווירה עם ombitasvir/paritaprevir/ritonavir ו-ribavirin:
תופעות לוואי שכיחות מאד (תופעות שמופיעות ביותר ממשתמש אחד מתוך עשרה):

- תחושת עייפות כבדה (תשישות)
- בחילה
- גרד
- בעיות שינה (נדודי שינה)
- חולשה או תחושת חוסר אנרגיה

תופעות לוואי שכיחות (תופעות שמופיעות בעד משתמש אחד מתוך עשרה):
- אנמיה (מספר נמוך של תאי דם אדומים)

תופעות לוואי נדירות (תופעות שמופיעות בעד משתמש אחד מתוך 1,000):
- התנפחות של שכבות בעור אשר יכולה להשפיע על כל חלק בגוף, כולל הפנים, לשון או גרון, ועלולה להוביל לקשיים בבליעה או בנשימה (בצקת מקומית-אנגיואדמה).

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא.

ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות(www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי, או ע"י כניסה לקישור :
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. איך לאחסן את התרופה?

- מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם וטווח ראייתם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.
- אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי האריזה. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.
- **תנאי איחסון**: יש לאחסן מתחת ל- 30°C. אחסן באריזה המקורית.
- אין להשליך תרופות למי השפכים או לפסולת הביתית. שאל את הרוקח כיצד ניתן להפטר מתרופות שאינך זקוק להן עוד. נקיטת אמצעים אלו תעזור לשמור על הסביבה.

6. מידע נוסף

- **נוסף על החומר הפעיל התרופה מכילה גם** –
ליבת הטבליה:
Microcrystalline cellulose, copovidone, lactose monohydrade, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide/anhydrous colloidal silica.
ציפוי הטבליה:
Polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide yellow, iron oxide red and iron oxide black.

- **כיצד נראית התרופה ומה תוכן האריזה:**
טבליות אקסווירה הן טבליות מצופות אובליות, בצבע בז', המסומנות בכיתוב 'AV2'.
הטבליות ארוזות בבליסטר המכיל 2 טבליות לשימוש חד יומי.
כל קרטון מכיל 56 טבליות (הארוזות ב- 4 אריזות קרטון פנימיות. כל אריזה פנימית מכילה 14 טבליות).
- **בעל הרישום וכתובתו**: AbbVie Biopharmaceuticals Ltd. , רחוב החרש 4, הוד-השרון, ישראל

- **שם היצרן וכתובתו**:.AbbVie Ltd, אנגליה
- **עלון זה נבדק ואושר ע"י משרד הבריאות בתאריך:** יוני 2017, ועודכן בהתאם להוראות משרד הבריאות בתאריך: אפריל 2018.
- **מספר רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות**: 153-56-34256

לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.