▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions**.**

1. NAME OF THE MEDICINAL PRODUCT

Exviera 250 mg film-coated 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

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 Summary of Product Characteristics 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	Exviera + ombitasvir/paritaprevir/ritonavir	12 weeks
Genotype 1b, with compensated cirrhosis	Exviera + ombitasvir/paritaprevir/ritonavir + ribavirin	12 weeks
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.		

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). The safety and efficacy of dasabuvir have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B); however, no dose adjustment is expected to be required based on pharmacokinetic studies. 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 Summary of Product Characteristics.

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).

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.

Pregnancy and concomitant use with ribavirin

When dasabuvir is used in combination with ribavirin, women of childbearing potential or their male partners must use an effective form of contraception during the treatment and for 6 months after the treatment as recommended in the Summary of Product Characteristics for ribavirin. Refer to the Summary of Product Characteristics for ribavirin for additional information.

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. Early discontinuation may result in drug resistance, but implications for future therapy are not known.

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 Summary of Product Characteristics 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).

Hepatic impairment

No dose adjustment of Exviera and ombitasvir/paritaprevir/ritonavir is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of dasabuvir have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B); however, no dose adjustment is expected to be required based on pharmacokinetic studies.

Exviera should not be used in patients with severe hepatic impairment (Child Pugh C) (see sections 4.2 and 5.1).

HCV/HBV (Hepatitis B Virus) co-infection

The safety and efficacy of dasabuvir have not been established in patients with HCV/HBV co-infection.

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 Summary of Product Characteristics for details. (see also Table 2).

Medicinal products transported by the OATP family
Refer to the ombitasvir/paritaprevir/ritonavir Summary of Product Characteristics 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. Other CYP1A2 substrates (e.g. ciprofloxacin, theophylline and caffeine) and 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).

Potential for other medicinal products to affect the pharmacokinetics of dasabuvir

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%.

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 Summary of Product Characteristics.

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_{min}	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.
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)	
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).

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
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 5 mg single dose	Exviera + ombitasvir /paritaprevir/ritonavir	↔ R-warfarin	1.05 (0.95-1.17)	0.88 (0.81-0.95)	0.94 (0.84-1.05)	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalised ratio (INR) is recommended.
		↔ S-warfarin	0.96 (0.85-1.08)	0.88 (0.81-0.96)	0.95 (0.88-1.02)	
		↔ 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/ritonav	Not Studied. Expected: ↑ dabigatran etexilate				Exviera + ombitasvir/paritaprevir/ritonavir may increase the plasma concentrations of dabigatran etexilate. Use with caution.
ANTICONVULSANTS						
carbamazepine 200 mg once daily followed by 200 mg twice daily Mechanism: CYP3A4 induction by carbamazepine.	Exviera + ombitasvir /paritaprevir/ritonavir	↔ carbamazepine	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).
		↓ carbamazepine 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).

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Phenytoin Mechanism: CYP3A4 induction by phenytoin.	Exviera + ombitasvir /paritapre vir/ritonav ir	Not studied. Expected: ↓ dasabuvir ↓ paritaprevir ↓ ombitasvir				Concomitant use is contraindicated (see section 4.3).
S-mephenytoin Mechanism: CYP2C19 induction by ritonavir.	Exviera + ombitasvir /paritapre vir/ritonav ir	Not studied. Expected: ↓ S-mephenytoin				Clinical monitoring and dose adjustment maybe needed for s-mephenytoin.
ANTIDEPRESSANTS						
Escitalopram 10 mg single dose	Exviera + ombitasvir/ paritaprevi r/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/ paritaprevi r/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/rit onavir.
		↔ 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 + ombitasvi r/paritapre vir/ ritonavir	↑ keto-conazole	1.15 (1.09-1.21)	2.17 (2.05-2.29)	NA	Concomitant use is contraindicated (see the Summary of Product Characteristics 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	
ANTIHYPERLIPIDAEMICS						
Gemfibrozil 600 mg twice	Exviera + paritaprev	↑ dasabuvir	2.01 (1.71-2.38)	11.25 (9.05-13.99)	NA	Concomitant use is contraindicated (see

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
daily Mechanism: Increase in dasabuvir exposure is due to CYP2C8 inhibition and increase in paritaprevir is possibly due to OATP1B1 inhibition by gemfibrozil.	ir/ ritonavir	↑ paritaprevir	1.21 (0.94-1.57)	1.38 (1.18-1.61)	NA	section 4.3).
ANTIMYCOBACTERIALS						
Rifampicin Mechanism: CYP3A4/CY P2C8 induction by rifampicin.	Exviera + Ombitasvi r/paritapre vir /ritonavir	Not Studied. Expected: ↓ dasabuvir ↓ ombitasvir ↓ paritaprevir				Concomitant use is contra-indicated (see section 4.3).
CALCIUM CHANNEL BLOCKERS						
Amlodipine 5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir.	Exviera + ombitasvi r/paritapre vir/ritona vir	↑ 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)	
		↓ paritaprevir	0.77 (0.64-0.94)	0.78 (0.68-0.88)	0.88 (0.80-0.95)	
CONTRACEPTIVES						
ethinylestradi ol/ norgestimate 0.035/0.25 mg once daily Mechanism: possibly due to UGT inhibition by paritaprevir, ombitasvir and dasabuvir.	Exviera + ombitasvi r/paritapre vir/ritona vir	↔ 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-elgestromin e	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)	Exviera + ombitasvi r/paritapre vir/ritona	↔ 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 +
		↔ dasabuvir	1.01 (0.90-1.14)	0.96 (0.85-1.09)	0.95 (0.80-1.13)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
0.35 mg once daily	vir	↔ ombitasvir	1.00 (0.93-1.08)	0.99 (0.94-1.04)	0.97 (0.90-1.03)	ombitasvir/paritaprevir/ritonavir.
		↑ 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)	
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 Summary of Product Characteristics of ombitasvir/ paritaprevir /ritonavir.						
Atazanavir 300 mg once daily (given at the same time)	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
		↔ 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATPs by atazanavir.		↑ paritaprevir	1.46 (1.06-1.99)	1.94 (1.34-2.81)	3.26 (2.06-5.16)	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.
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	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
		↔ 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
time) Mechanism: Unknown		↑ paritaprevir	1.54 (1.14-2.09)	1.29 (1.04-1.61)	1.30 (1.09-1.54)	(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.
Darunavir/ ritonavir 600/100 mg twice daily Mechanism: Unknown	Exviera + ombitasvir/paritaprevir/ritonavir	↔ darunavir	0.87 (0.79-0.96)	0.80 (0.74-0.86)	0.57 (0.48-0.67)	
		↓ 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]	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/rit
		↔ dasabuvir	0.99 (0.75-1.31)	0.93 (0.75-1.15)	0.68 (0.57-0.80)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Mechanism: Increase in paritaprevir exposures may be due to inhibition of CYP3A/efflux transporters by lopinavir and higher dose of ritonavir.		↔ ombitasvir	1.14 (1.01-1.28)	1.17 (1.07-1.28)	1.24 (1.14-1.34)	onavir due to increase in paritaprevir exposures (see Summary of Product Characteristics of ombitasvir/paritaprevir/ritonavir).
		↑ 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 food Mechanism: CYP3A inhibition by ritonavir.	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 section 4.4. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	1.18 (1.02-1.37)	1.17 (0.99-1.38)	1.10 (0.89-1.37)	
		↔ ombitasvir	1.11 (1.02-1.20)	1.09 (1.04-1.14)	1.05 (1.01-1.08)	
		↑ paritaprevir	1.30 (0.94-1.81)	1.23 (0.93-1.64)	0.95 (0.84-1.07)	
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						
Raltegravir	Exviera +	↑ raltegravir	2.33	2.34	2.00	No dose adjustment is

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
400 mg twice daily Mechanism: UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	ombitasvir/paritaprevir/ritonavir		(1.66-3.27)	(1.70-3.24)	(1.17-3.42)	necessary for raltegravir or Exviera + ombitasvir/paritaprevir/ritonavir.
		No clinically relevant changes in dasabuvir, paritaprevir, and ombitasvir exposures (based on comparison with historical data) were observed during the co-administration.				
HIV ANTIVIRALS: NUCLEOSIDE INHIBITORS						
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 paritaprevir and BCRP inhibition by dasabuvir paritaprevir, and ritonavir.	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)	
		↑ 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)	NA	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	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

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Mechanism: OATP1B inhibition by paritaprevir.						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: 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.	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. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↓ 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)	
		↑ paritaprevir	1.44 (1.16-1.78)	1.72 (1.49-1.99)	1.85 (1.58-2.18)	
Tacrolimus 2 mg single dose[4] 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)	When starting co-administration with dasabuvir and ombitasvir/paritaprevir/ritonavir administer 0.5 mg tacrolimus once every week. Monitor tacrolimus levels and adjust dose and/or dosing frequency as needed. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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 Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
MEDICINAL PRODUCTS USED IN MULTIPLE SCLEROSIS						
Teriflunomide	Exviera + ombitasvir /paritapre vir/ritonav ir	Not studied. Expected: ↑ dasabuvir				Teriflunomide may increase dasabuvir exposures and should be used with caution.
OPIOIDS						
Methadone 20-120 mg once daily[5]	Exviera + ombitasvi r/paritapre vir/ritona vir	↔ 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/rit onavir.
		↔ 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)				
buprenorphin e/ naloxone 4-24 mg/1-6 mg once daily[5] Mechanism: CYP3A4 inhibition by ritonavir and UGT inhibition by paritaprevir, ombitasvir and dasabuvir.	Exviera + ombitasvi r/paritapre vir/ritona vir	↑ bu-prenorphine	2.18 (1.78-2.68)	2.07 (1.78-2.40)	3.12 (2.29-4.27)	No dose adjustment is necessary for buprenorphine/naloxone and Exviera + ombitasvir/paritaprevir/rit onavir.
		↑ 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)				
PROTON PUMP INHIBITORS						
Omeprazole 40 mg once daily Mechanism: CYP2C19 induction by ritonavir.	Exviera + ombitasvi r/paritapre vir/ritona vir	↓ 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/rit onavir.
		↔ 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 /paritapre vir/ritonav ir	Not studied. Expected: ↓ esomeprazole, lansoprazole				If clinically indicated, higher doses of esomeprazole/lansoprazol e may be needed.
SEDATIVES / HYPNOTICS						
Zolpidem	Exviera + ombitasvi	↔ zolpidem	0.94 (0.76-1.16)	0.95 (0.74-1.23)	NA	No dose adjustment is

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
5 mg single dose	r/paritaprevir/ritonavir	↔ dasabuvir	0.93 (0.84-1.03)	0.95 (0.84-1.08)	0.92 (0.83-1.01)	necessary for zolpidem. No dose adjustment needed for Exviera + ombitasvir/paritaprevir/ritonavir.
		↔ 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)	
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_{min}	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. 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.
5. 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, rosuvastatin and pravastatin.

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. Women of childbearing potential and their male partners should not receive ribavirin unless they are using an effective form of contraception during treatment with ribavirin and for 6 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 Summary of Product Characteristics 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 Summary of Product Characteristics 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.

Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin (including subjects with compensated cirrhosis)

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). 0.2% (5/2,044) of subjects interrupted treatment due to adverse reactions. 4.8% (99/2,044) of subjects had ribavirin dose reductions due to adverse reactions.

With the exception of increased rates of transient hyperbilirubinemia, the safety profile of Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin in subjects with compensated cirrhosis was similar to that of subjects without cirrhosis.

Exviera and ombitasvir/paritaprevir/ritonavir without ribavirin:

No subjects permanently discontinued treatment or had treatment interruptions due to adverse reactions.

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
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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme:

Website: www.mhra.gov.uk/yellowcard

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: not yet assigned

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 Summary of Product Characteristics 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 six randomised Phase 3 clinical trials, including one trial exclusively in subjects with compensated cirrhosis (Child-Pugh A), in over 2,300 subjects with genotype 1 chronic hepatitis C infection as summarised in Table 6.

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

Trial[1]	Number of subjects treated[2]	HCV genotype (GT)	Summary of study design[3]
Treatment-naïve[4], 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
Peginteferon+ribavirin-experienced[5], 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)

1. Double-blind unless otherwise noted.
2. Treated is defined as subjects who were randomised and received at least one dose of Exviera and ombitasvir/paritaprevir/ritonavir.
3. Treatment duration was 12 weeks for all arms, except for TURQUOISE II which included a 24 week arm.
4. Treatment naïve was defined as not having received any prior therapy for HCV infection.
5. Peginterferon+ribavirin -experienced subjects were defined as either: prior relapsers (subjects with HCV RNA undetectable at or after the end of at least 36 weeks of pegIFN/RBV treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up) or prior partial responders (received at least 20 weeks of pegIFN/RBV and achieved a greater than or equal to 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment) or prior null-responders (received at least 12 weeks of pegIFN/RBV treatment and failed to achieve a 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 or received at least 4 weeks of pegIFN/RBV treatment and achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at week 4).

In all six 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. The assay had a lower limit of quantification (LLOQ) of 25 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[b]	7/463	1.5	
Other[c]	9/473	1.9	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. 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[a]	1/210	0.5		0/209	0	
Relapse[b]	0/210	0		0/209	0	
Other[c]	0/210	0		0/209	0	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

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[a]	1/100	1.0		6/205	2.9	
Relapse[b]	1/98	1.0		10/194	5.2	
Other[c]	1/100	1.0		4/205	2.0	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

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 10 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 10. 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[a]	0/297	0	
Relapse[b]	7/293	2.4	
Other[c]	4/297	1.3	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

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 11 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 11. 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[a]	0/88	0		0/91	0	
Relapse[b]	0/88	0		0/91	0	
Other[c]	2/88	2.3		0/91	0	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR4 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

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

Table 12. 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[b]	1/208	0.5		3/172	1.7	
Relapse[c]	12/203	5.9		1/164	0.6	
Other[d]	4/208	1.9		2/172	1.21	

CI = confidence interval, VF = virologic failure

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).

b. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

c. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 or 22 weeks of treatment, for subjects assigned to 12 or 24 weeks of treatment, respectively.

d. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Relapse rates in GT1a cirrhotic subjects by baseline laboratory values are presented in Table 13.

Table 13. 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.

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, 1083 subjects (including 189 with compensated cirrhosis) received the recommended regimen for their HCV genotype 1 subtype, cirrhosis status and relevant baseline characteristics. Table 14 shows SVR rates for these subjects.

In subjects who received the recommended regimen, 97% achieved SVR overall (among which 189 subjects with compensated cirrhosis achieved 96% SVR), while 0.5% experienced virologic breakthrough and 1.3% experienced post-treatment relapse.

Table 14. SVR12 rates for recommended treatment regimens by patient population

	HCV Genotype 1b		HCV Genotype 1a	
	Without cirrhosis **ombitasvir/ paritaprevir/ ritonavir and Exviera**	**With compensated cirrhosis** **ombitasvir/ paritaprevir/ ritonavir and Exviera with RBV**	**Without cirrhosis** **ombitasvir/ paritaprevir/ ritonavir and Exviera with RBV**	**With compensated cirrhosis** **ombitasvir/ paritaprevir/ ritonavir and Exviera with RBV**
	12 weeks	**12 weeks**	**12 weeks**	**24 weeks**
Treatment-naïve	100% (210/210)	100% (22/22)	96% (403/420)	95% (53/56)
pegIFN + RBV-experienced	100% (91/91)	98% (45/46)	96% (166/173)	95% (62/65)
Prior relapse	100% (33/33)	100% (14/14)	94% (47/50)	100% (13/13)
Prior partial response	100% (26/26)	86% (6/7)	100% (36/36)	100% (10/10)
Prior null response	100% (32/32)	100% (25/25)	95% (83/87)	93% (39/42)
TOTAL	100% (301/301)	99% (67/68)	96% (569/593)	95% (115/121)

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

Table 15. 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[a]	0	1
Post-treatment relapse[b]	1	2[c]
Other[d]	1	0

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

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

d. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Exviera and ombitasvir/paritaprevir/ritonavir in one or more subsets of the paediatric populations in the treatment of chronic hepatitis C (see section 4.2 for information on paediatric use).

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 16 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 16. 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 μg/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.

The changes in dasabuvir exposures in subjects with mild and moderate hepatic impairment are not considered clinically significant. The safety and efficacy of Exviera and ombitasvir/paritaprevir/ritonavir have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B) (see section 4.2).

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 39-fold higher than those in humans at the recommended dose of 500 mg (250 mg twice daily).

The carcinogenicity study of dasabuvir in rats is ongoing.

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 33 to 48-fold (rat) or 12-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 (E460(i))
Lactose monohydrate
Copovidone
Croscarmellose sodium
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)

Film-coating
Polyvinyl alcohol (E1203)

Titanium dioxide (E171)
Polyethylene glycol 3350
Talc (E553b)
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 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).

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4XE
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/983/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 January 2015

10. DATE OF REVISION OF THE TEXT

01/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.