ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 45 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 dasabuvir should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

Posology

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

Dasabuvir must not be administered as monotherapy. Dasabuvir 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 dasabuvir.

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

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

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

Missed doses
In case a dose of dasabuvir is missed, the prescribed dose can be taken within 6 hours. If more than 6 hours have passed since dasabuvir 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
The dosing recommendations in Table 1 should be followed. For dosing recommendations with HIV antiviral medicinal products, refer to sections 4.4 and 4.5. See sections 4.8 and 5.1 for additional information.

Liver transplant recipients
Dasabuvir 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 dasabuvir is warranted in elderly patients (see section 5.2).

Renal impairment

No dose adjustment of dasabuvir is required for patients with mild, moderate, or severe renal impairment or end-stage-renal disease on dialysis (see section 5.2). For patients that require ribavirin, refer to the ribavirin Summary of Product Characteristics for information regarding use in patients with renal impairment.

Hepatic impairment

No dose adjustment of dasabuvir is required in patients with mild hepatic impairment (Child-Pugh A). Dasabuvir should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or 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, dasabuvir tablets should be taken with food, without regard to fat and calorie content (see section 5.2).

4.3 Contraindications

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

Patients with moderate to severe hepatic impairment (Child-Pugh B or C) (see section 5.2).

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

Co-administration of dasabuvir 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
- apalutamide, 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 dasabuvir (see section 4.5). Examples of contraindicated CYP2C8 inhibitors are provided below.

CYP2C8 inhibitor:

- gemfibrozil

Dasabuvir 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

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

Risk of hepatic decompensation and hepatic failure in patients with cirrhosis

Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported post-marketing in patients treated with dasabuvir with ombitasvir/paritaprevir/ritonavir with and without ribavirin. Most patients with these severe outcomes had evidence of advanced or decompensated cirrhosis prior to initiating therapy. Although causality is difficult to establish due to background advanced liver disease, a potential risk cannot be excluded.

Dasabuvir should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C) (see sections 4.2, 4.3, 4.8 and 5.2).

For patients with cirrhosis:

- Monitoring should be performed for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal haemorrhage).
- Hepatic laboratory testing including direct bilirubin levels should be performed at baseline, during the first 4 weeks of starting treatment and as clinically indicated thereafter.
- Treatment should be discontinued in patients who develop evidence of hepatic decompensation.

ALT elevations

During clinical trials with dasabuvir and ombitasvir/paritaprevir/ritonavir with or without ribavirin, transient elevations of ALT to greater than 5 times the upper limit of normal occurred in approximately 1% of subjects (35 of 3,039). ALT elevations were asymptomatic and generally occurred during the first 4 weeks of treatment, without concomitant elevations of bilirubin, and declined within approximately two weeks of onset with continued dosing of dasabuvir and ombitasvir/paritaprevir/ritonavir with or without ribavirin.

These ALT elevations were significantly more frequent in the subgroup of subjects who were using ethinyloestradiol -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 oestrogens as typically used in hormonal replacement therapy (i.e., oral and topical oestradiol and conjugated oestrogens) was similar to the rate observed in subjects who were not using oestrogen-containing products (approximately 1% in each group).

Patients who are taking ethinyloestradiol -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 dasabuvir with ombitasvir/paritaprevir/ritonavir therapy (see sections 4.3 and 4.5).

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

Pregnancy and concomitant use with ribavirin

Also see section 4.6.

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients when dasabuvir is taken in combination with ribavirin (see section 4.6 and refer to the Summary of Product Characteristics for ribavirin for additional information).

Use with tacrolimus, sirolimus and everolimus

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

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

Tacrolimus or sirolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with dasabuvir and ombitasvir/paritaprevir/ritonavir and the dose and/or dosing frequency should be adjusted as needed. Patients should be monitored frequently for any changes in renal function or tacrolimus or sirolimus associated adverse reactions. Refer to the tacrolimus or sirolimus Summary of Product Characteristics for additional dosing and monitoring instructions.

Depression or psychiatric illness

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

Genotype-specific activity

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

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

Co-administration with other direct-acting antivirals against HCV

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

Retreatment

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

Use with statins

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

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

Treatment of patients with HIV co-infection

Dasabuvir 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).

Hepatitis B virus reactivation

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

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct acting antiviral treatment. Glucose levels of diabetic patients initiating direct acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medicinal products modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct acting antiviral therapy is initiated.

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Lactose

Exviera contains lactose. Patients with rare hereditary problems of galactose intolerance, total 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 ethinyloestradiol 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 dasabuvir 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 dasabuvir 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 dasabuvir with ombitasvir/paritaprevir/ritonavir. It may not be excluded that the systemic exposure of dabigatran etexilate is increased by dasabuvir due to inhibition of P-gp in the intestine.

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

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

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

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

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

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

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

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

Enzyme inducers

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

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

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

Patients treated with vitamin K antagonists

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

Drug interaction studies

Recommendations for co-administration of dasabuvir 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 dasabuvir 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 dasabuvir and ombitasvir/paritaprevir/ritonavir, doses should be re-adjusted after administration of dasabuvir 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. Dasabuvir is administered with ombitasvir/paritaprevir/ritonavir. For interactions with ombitasvir/ paritaprevir /ritonavir refer to the Summary of Product Characteristics.

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

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

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Sulfasalazine Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not Studied. Expected: ↑ sulfasalazine				Caution should be used when sulfasalazine is co-administered with dasabuvir + ombitasvir/paritaprevir/ritonavir.
ANTIARRYTHMICS						
Digoxin 0.5 mg single dose Mechanism: P-gp inhibition by dasabuvir, paritaprevir, and ritonavir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	↔ digoxin	1.15 (1.04-1.27)	1.16 (1.09-1.23)	1.01 (0.97-1.05)	While no dose adjustment is necessary for digoxin, appropriate monitoring of serum digoxin levels is recommended.
		↔ dasabuvir	0.99 (0.92-1.07)	0.97 (0.91-1.02)	0.99 (0.92-1.07)	
		↔ ombitasvir	1.03 (0.97-1.10)	1.00 (0.98-1.03)	0.99 (0.96-1.02)	
		↔ paritaprevir	0.92 (0.80-1.06)	0.94 (0.81-1.08)	0.92 (0.82-1.02)	
ANTIBIOTICS (SYSTEMIC ADMINISTRATION)						
Sulfameth-oxazole, trimethoprim 800/160 mg twice daily Mechanism: increase in dasabuvir possibly due to CYP2C8 inhibition by trimethoprim	dasabuvir + ombitasvir/paritaprevir/ritonavir	↑ Sulfameth-oxazole,	1.21 (1.15-1.28)	1.17 (1.14-1.20)	1.15 (1.10-1.20)	No dose adjustment needed for dasabuvir + ombitasvir/paritaprevir/ritonavir.
		↑ trimethoprim	1.17 (1.12-1.22)	1.22 (1.18-1.26)	1.25 (1.19-1.31)	
		↑ dasabuvir	1.15 (1.02-1.31)	1.33 (1.23-1.44)	NA	
		↔ ombitasvir	0.88 (0.83-0.94)	0.85 (0.80-0.90)	NA	
		↓ paritaprevir	0.78 (0.61-1.01)	0.87 (0.72-1.06)	NA	
ANTICANCER AGENTS						
Apalutamide Enzalutamide Mitotane Mechanism: CYP3A4 induction by apalutamide, enzalutamide or mitotane.	dasabuvir + 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_{trough}	Clinical Comments
Imatinib Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not Studied. Expected: ↑ imatinib				Clinical monitoring and lower doses of imatinib are recommended.
ANTICOAGULANTS						
Warfarin 5 mg single dose and other vitamin K antagonists	dasabuvir + 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 change in the pharmacokinetics of warfarin is expected, close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with dasabuvir + ombitasvir/paritaprevir/ritonavir
		↔ 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.	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not Studied. Expected: ↑ dabigatran etexilate				dasabuvir + 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.	dasabuvir + 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	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Phenobarbital Mechanism: CYP3A4 induction by phenobarbital.	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not studied. Expected: ↓ dasabuvir ↓ paritaprevir ↓ ombitasvir				Concomitant use is contraindicated (see section 4.3).
Phenytoin Mechanism: CYP3A4 induction by phenytoin.	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not studied. Expected: ↓ dasabuvir ↓ paritaprevir ↓ ombitasvir				Concomitant use is contraindicated (see section 4.3).
S-mephenytoin Mechanism: CYP2C19 induction by ritonavir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not studied. Expected: ↓ S-mephenytoin				Clinical monitoring and dose adjustment maybe needed for s-mephenytoin.
ANTIDEPRESSANTS						
Escitalopram 10 mg single dose	dasabuvir + ombitasvir/paritaprevir/ritonavir	↔ es-citalopram	1.00 (0.96-1.05)	0.87 (0.80-0.95)	NA	No dose adjustment is necessary for escitalopram.
		↑ S-Desmethyl citalopram	1.15 (1.10-1.21)	1.36 (1.03-1.80)	NA	
		↔ dasabuvir	1.10 (0.95-1.27)	1.01 (0.93-1.10)	0.89 (0.79-1.00)	
		↔ ombitasvir	1.09 (1.01-1.18)	1.02 (1.00-1.05)	0.97 (0.92-1.02)	
		↔ paritaprevir	1.12 (0.88-1.43)	0.98 (0.85-1.14)	0.71 (0.56-0.89)	
Duloxetine 60 mg single dose	dasabuvir + ombitasvir/paritaprevir/ritonavir	↓ duloxetine	0.79 (0.67-0.94)	0.75 (0.67-0.83)	NA	No dose adjustment is necessary for duloxetine. No dose adjustment needed for dasabuvir + ombitasvir/paritaprevir /ritonavir.
		↔ dasabuvir	0.94 (0.81-1.09)	0.92 (0.81-1.04)	0.88 (0.76-1.01)	
		↔ ombitasvir	0.98 (0.88-1.08)	1.00 (0.95-1.06)	1.01 (0.96-1.06)	
		↓ paritaprevir	0.79 (0.53-1.16)	0.83 (0.62-1.10)	0.77 (0.65-0.91)	
ANTIFUNGALS						
Ketoconazole 400 mg once daily Mechanism: CYP3A4/P-gp inhibition by ketoconazole	dasabuvir + ombitasvir/paritaprevir/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	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
and paritaprevir/ ritonavir/ ombitasvir						
ANTIHYPERLIPIDAEMICS						
Gemfibrozil 600 mg twice daily Mechanism: Increase in dasabuvir exposure is due to CYP2C8 inhibition and increase in paritaprevir is possibly due to OATP1B1 inhibition by gemfibrozil.	dasabuvir + paritaprevir/ ritonavir	↑ dasabuvir	2.01 (1.71-2.38)	11.25 (9.05-13.99)	NA	Concomitant use is contraindicated (see section 4.3).
		↑ paritaprevir	1.21 (0.94-1.57)	1.38 (1.18-1.61)	NA	
ANTIMYCOBACTERIALS						
Rifampicin Mechanism: CYP3A4/CYP2C8 induction by rifampicin.	dasabuvir + Ombitasvir/paritaprevir /ritonavir	Not Studied. Expected: ↓ dasabuvir ↓ ombitasvir ↓ paritaprevir				Concomitant use is contra-indicated (see section 4.3).
BIGUANIDE ORAL ANTIHYPERGLYCEMICS						
Metformin 500 mg single dose	dasabuvir + ombitasvir/paritaprevir/ritonavir	↓ metformin	0.77 (0.71-0.83)	0.90 (0.84-0.97)	NA	No dose adjustment needed for metformin when co-administered with dasabuvir + ombitasvir/paritaprevir/ ritonavir.
		↔ dasabuvir	0.83 (0.74-0.93)	0.86 (0.78-0.94)	0.95 (0.84-1.07)	
		↔ ombitasvir	0.92 (0.87-0.98)	1.01 (0.97-1.05)	1.01 (0.98-1.04)	
		↓ paritaprevir	0.63 (0.44-0.91)	0.80 (0.61-1.03)	1.22 (1.13-1.31)	
CALCIUM CHANNEL BLOCKERS						
Amlodipine 5 mg single dose	dasabuvir + ombitasvir/paritaprevir/	↑ amlodipine	1.26 (1.11-1.44)	2.57 (2.31-2.86)	NA	Decrease in amlodipine dose by 50% and monitor patients for clinical effects.
		↔ dasabuvir	1.05 (0.97-1.14)	1.01 (0.96-1.06)	0.95 (0.89-1.01)	
		↔ ombitasvir	1.00 (0.95-1.06)	1.00 (0.97-1.04)	1.00 (0.97-1.04)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Mechanism: CYP3A4 inhibition by ritonavir.	ritonavir	↓ paritaprevir	0.77 (0.64-0.94)	0.78 (0.68-0.88)	0.88 (0.80-0.95)	
CONTRACEPTIVES						
ethinyloestradiol/ norgestimate 0.035/0.25 mg once daily Mechanism: possibly due to UGT inhibition by paritaprevir, ombitasvir and dasabuvir.	dasabuvir + ombitasvir/paritaprevir/ ritonavir	↔ ethinyl oestradiol	1.16 (0.90-1.50)	1.06 (0.96-1.17)	1.12 (0.94-1.33)	Ethinyloestradiol containing oral contraceptives are contraindicated (see section 4.3).
		Norgestimate metabolites:				
		↑ norgestrel	2.26 (1.91-2.67)	2.54 (2.09-3.09)	2.93 (2.39-3.57)	
		↑ nor-elgestromine	2.01 (1.77-2.29)	2.60 (2.30-2.95)	3.11 (2.51-3.85)	
		↓ dasabuvir	0.51 (0.22-1.18)	0.48 (0.23-1.02)	0.53 (0.30- 0.95)	
		↔ ombitasvir	1.05 (0.81-1.35)	0.97 (0.81-1.15)	1.00 (0.88- 1.12)	
		↓ paritaprevir	0.70 (0.40-1.21)	0.66 (0.42-1.04)	0.87 (0.67-1.14)	
nor-ethindrone (progestin only pill) 0.35 mg once daily	dasabuvir + ombitasvir/paritaprevir/ ritonavir	↔ nor-ethindrone	0.83 (0.69-1.01)	0.91 (0.76-1.09)	0.85 (0.64-1.13)	No dose adjustment is necessary for norethindrone or dasabuvir + ombitasvir/paritaprevir/ ritonavir.
		↔ dasabuvir	1.01 (0.90-1.14)	0.96 (0.85-1.09)	0.95 (0.80-1.13)	
		↔ ombitasvir	1.00 (0.93-1.08)	0.99 (0.94-1.04)	0.97 (0.90-1.03)	
		↑ paritaprevir	1.24 (0.95-1.62)	1.23 (0.96-1.57)	1.43 (1.13-1.80)	
DIURETICS						
Furosemide 20 mg single dose Mechanism: possibly due to UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	dasabuvir + 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 dasabuvir + 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
HCV ANTIVIRAL						
Sofosbuvir 400 mg once daily Mechanism: BCRP and P-gp inhibition by paritaprevir, ritonavir and dasabuvir	dasabuvir + ombitasvir/paritaprevir/ritonavir	↑ sofosbuvir	1.61 (1.38-1.88)	2.12 (1.91-2.37)	NA	No dose adjustment needed for sofosbuvir when administered with dasabuvir + ombitasvir/paritaprevir /ritonavir.
		↑ GS-331007	1.02 (0.90-1.16)	1.27 (1.14-1.42)	NA	
		↔ dasabuvir	1.09 (0.98-1.22)	1.02 (0.95-1.10)	0.85 (0.76-0.95)	
		↔ ombitasvir	0.93 (0.84-1.03)	0.93 (0.87-0.99)	0.92 (0.88-0.96)	
		↔ paritaprevir	0.81 (0.65-1.01)	0.85 (0.71-1.01)	0.82 (0.67-1.01)	
HERBAL PRODUCTS						
St. John's Wort (*hypericum perforatum*) Mechanism: CYP3A4 induction by St. John's Wort.	dasabuvir + 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)	dasabuvir + 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 dasabuvir + ombitasvir/paritaprevir/ ritonavir. Atazanavir
		↔ 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_{trough}	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)	must be administered at the same time as dasabuvir +ombitasvir/paritaprevir/ritonavir. Ritonavir dose in ombitasvir/paritaprevir/ritonavir will provide atazanavir pharmacokinetic enhancement. No dose adjustment needed for dasabuvir + 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	dasabuvir + ombitasvir/parit	↔ 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
(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.	aprevir/ritonavir	↑ 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	dasabuvir + ombitasvir/paritaprevir/	↓ 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
		↔ 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_{trough}	Clinical Comments
at the same time) Mechanism: Unknown	ritonavir	↑ paritaprevir	1.54 (1.14-2.09)	1.29 (1.04-1.61)	1.30 (1.09-1.54)	same time as ombitasvir/paritaprevir/ ritonavir + dasabuvir (ritonavir dose in ombitasvir/paritaprevir/ ritonavir will provide darunavir pharmacokinetic enhancement). This regimen can be used in the absence of extensive PI resistance (i.e. lack of darunavir associated RAMs), see also section 4.4. Darunavir combined with ombitasvir/paritaprevir/ ritonavir + dasabuvir is not recommended in patients with extensive PI resistance. No dose adjustment needed for dasabuvir + ombitasvir/paritaprevir/ ritonavir.
Darunavir/ ritonavir 600/100 mg twice daily Mechanism: Unknown	dasabuvir + 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	dasabuvir + 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	dasabuvir +	↔ 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

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
400/100 mg twice daily[1] Mechanism: Increase in paritaprevir exposures may be due to inhibition of CYP3A/efflux transporters by lopinavir and higher dose of ritonavir.	ombitasvir/paritaprevir/ritonavir	↔ dasabuvir	0.99 (0.75-1.31)	0.93 (0.75-1.15)	0.68 (0.57-0.80)	or 800/200 mg once daily is contraindicated with dasabuvir and ombitasvir/paritaprevir/ritonavir due to increase in paritaprevir exposures (see Summary of Product Characteristics of ombitasvir/paritaprevir/ritonavir).
		↔ ombitasvir	1.14 (1.01-1.28)	1.17 (1.07-1.28)	1.24 (1.14-1.34)	
		↑ paritaprevir	2.04 (1.30-3.20)	2.17 (1.63-2.89)	2.36 (1.00-5.55)	
HIV ANTIVIRALS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS						
Rilpivirine[2] 25 mg once daily administered in the morning, with food Mechanism: CYP3A inhibition by ritonavir.	dasabuvir + 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 dasabuvir 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 dasabuvir + 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	dasabuvir + 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).

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Mechanism: possible enzyme induction by efavirenz.						
Nevirapine etravirine	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not Studied. Expected: ↓ dasabuvir ↓ ombitasvir ↓ paritaprevir				Concomitant use is contraindicated (see section 4.3).
HIV ANTIVIRALS: INTEGRASE STRAND TRANSFER INHIBITOR						
Dolutegravir 50 mg once daily Mechanism: possibly due to UGT1A1 inhibition by paritaprevir, dasabuvir and ombitasvir and CYP3A4 inhibition by ritonavir	dasabuvir + ombitasvir/paritaprevir/ritonavir	↑ dolutegravir	1.22 (1.15-1.29)	1.38 (1.30-1.47)	1.36 (1.19-1.55)	No dose adjustment needed for dolutegravir when administered with dasabuvir + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	1.01 (0.92-1.11)	0.98 (0.92-1.05)	0.92 (0.85-0.99)	
		↔ ombitasvir	0.96 (0.89-1.03)	0.95 (0.90-1.00)	0.92 (0.87-0.98)	
		↔ paritaprevir	0.89 (0.69-1.14)	0.84 (0.67-1.04)	0.66 (0.59-0.75)	
Raltegravir 400 mg twice daily Mechanism: UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	↑ raltegravir	2.33 (1.66-3.27)	2.34 (1.70-3.24)	2.00 (1.17-3.42)	No dose adjustment is necessary for raltegravir or dasabuvir + 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						
Abacavir/ lamivudine	dasabuvir + ombitasvir/paritaprevir/ritonavir	↔ abacavir	0.87 (0.78-0.98)	0.94 (0.90-0.99)	NA	No dose adjustment needed for abacavir or lamivudine when administered with dasabuvir +
		↓ lamivudine	0.78 (0.72-0.84)	0.88 (0.82-0.93)	1.29 (1.05-1.58)	
		↔ dasabuvir	0.94 (0.86-1.03)	0.91 (0.86-0.96)	0.95 (0.88-1.02)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
600/300 mg once daily		↔ ombitasvir	0.82 (0.76-0.89)	0.91 (0.87-0.95)	0.92 (0.88-0.96)	ombitasvir/paritaprevir/ ritonavir.
		↔ paritaprevir	0.84 (0.69-1.02)	0.82 (0.70-0.97)	0.73 (0.63-0.85)	
Em-tricitabine/ tenofovir 200 mg once daily/300 mg once daily	dasabuvir + 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 dasabuvir + 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.	dasabuvir + 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 dasabuvir + 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.	dasabuvir + ombitasvir/paritaprevir/ritonavir	↑ pravastatin	1.37 (1.11-1.69)	1.82 (1.60-2.08)		Reduce pravastatin dose by 50%. No dose adjustment needed for dasabuvir + ombitasvir/paritaprevir /ritonavir.
		↔ dasabuvir	1.00 (0.87-1.14)	0.96 (0.85-1.09)	1.03 (0.91-1.15)	
		↔ ombitasvir	0.95 (0.89-1.02)	0.94 (0.89-0.99)	0.94 (0.89-0.99)	
		↔ paritaprevir	0.96 (0.69-1.32)	1.13 (0.92-1.38)	1.39 (1.21-1.59)	
Fluvastatin Mechanism: OATP1B/BCRP inhibition by paritaprevir. Pitavastatin Mechanism:	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not studied. Expected: ↑ fluvastatin ↑ pitavastatin ↔ dasabuvir ↔ ombitasvir ↔ paritaprevir				Concomitant use with fluvastatin and pitavastatin is not recommended (see section 4.4). A temporary suspension of fluvastatin and pitavastatin is recommended for the duration of treatment. If statin treatment is

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
OATP1B inhibition by paritaprevir.						required during the treatment period, a switch to dose reduced pravastatin or rosuvastatin is possible. No dose adjustment needed for dasabuvir + 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.	dasabuvir + 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 dasabuvir 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 dasabuvir + 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)	
Everolimus 0.75 mg single dose Mechanism: Effect on everolimus is due to CYP3A4 inhibition by ritonavir.	dasabuvir + ombitasvir/paritaprevir/ ritonavir	↑ everolimus	4.74 (4.29-5.25)	27.1 (24.5-30.1)	16.1 (14.5-17.9)[4]	Co-administration of dasabuvir + ombitasvir/paritaprevir/ ritonavir with everolimus is not recommended because of a significant increase in everolimus exposures which cannot be properly dose adjusted with available dose strengths.
		↔ dasabuvir	1.03 (0.90-1.18)	1.08 (0.98-1.20)	1.14 (1.05-1.23)	
		↔ ombitasvir	0.99 (0.95-1.03)	1.02 (0.99-1.05)	1.02 (0.99-1.06)	
		↔ paritaprevir	1.22 (1.03-1.43)	1.26 (1.07-1.49)	1.06 (0.97-1.16)	
Sirolimus	dasabuvir + ombitas	↑ Sirolimus	6.40 (5.34-7.68)	38.0 (31.5-45.8)	19.6 (16.7-22.9)[6]	Concomitant use of sirolimus with dasabuvir +

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
0.5 mg single dose[5] Mechanism: Effect on sirolimus is due to CYP3A4 inhibition by ritonavir.	vir/paritaprevir/ritonavir	↔ dasabuvir	1.04 (0.89-1.22)	1.07 (0.95-1.22)	1.13 (1.01-1.25)	ombitasvir/paritaprevir/ritonavir is not recommended unless the benefits outweigh the risks (see section 4.4). If sirolimus is used together with dasabuvir + ombitasvir/paritaprevir/ritonavir, administer sirolimus 0.2 mg twice a week (every 3 or 4 days on the same two days each week). Sirolimus blood concentrations should be monitored every 4 to 7 days until 3 consecutive trough levels have shown stable concentrations of sirolimus. Sirolimus dose and/or dosing frequency should be adjusted as needed. 5 days after completion of dasabuvir + ombitasvir/paritaprevir/ritonavir treatment, the sirolimus dose and dosing frequency prior to receiving dasabuvir + ombitasvir/paritaprevir/ritonavir should be resumed, along with routine monitoring of sirolimus blood concentrations.
		↔ ombitasvir	1.03 (0.93-1.15)	1.02 (0.96-1.09)	1.05 (0.98-1.12)	
		↔ paritaprevir	1.18 (0.91-1.54)	1.19 (0.97-1.46)	1.16 (1.00-1.34)	
Tacrolimus 2 mg single dose[7] Mechanism: Effect on	dasabuvir + ombitasvir/paritaprevir/	↑ tacrolimus	3.99 (3.21-4.97)	57.1 (45.5-71.7)	16.6 (13.0-21.2)	Concomitant use of tacrolimus with dasabuvir and ombitasvir/paritaprevir/ritonavir is not recommended unless the benefits outweigh
		↔ 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)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
tacrolimus is due to CYP3A4 inhibition by ritonavir.	ritonavir	↓ paritaprevir	0.57 (0.42-0.78)	0.66 (0.54-0.81)	0.73 (0.66-0.80)	the risks (see section 4.4). If tacrolimus with dasabuvir and ombitasvir/paritaprevir/ ritonavir are used concomitantly, tacrolimus should not be administered on the day dasabuvir and ombitasvir/paritaprevir/ ritonavir are initiated. Beginning the day after dasabuvir and ombitasvir/paritaprevir/ ritonavir are initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. The recommended tacrolimus dosing is 0.5 mg every 7 days. Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with dasabuvir and ombitasvir/paritaprevir/ ritonavir and the dose and/or dosing frequency should be adjusted as needed. Upon completion of dasabuvir and ombitasvir/paritaprevir/ ritonavir treatment, the appropriate dose and dosing frequency of tacrolimus should be guided by assessment of tacrolimus blood concentrations.
IRON CHELATORS						

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Deferasirox	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not studied. Expected: ↑ dasabuvir				Deferasirox may increase dasabuvir exposures and should be used with caution.
MEDICINAL PRODUCTS USED IN MULTIPLE SCLEROSIS						
Teriflunomide	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not studied. Expected: ↑ dasabuvir				Teriflunomide may increase dasabuvir exposures and should be used with caution.
OPIOIDS						
Methadone 20-120 mg once daily[8]	dasabuvir + ombitasvir/paritaprevir/ritonavir	↔ R-Methadone	1.04 (0.98-1.11)	1.05 (0.98-1.11)	0.94 (0.87-1.01)	No dose adjustment is necessary for methadone and dasabuvir + ombitasvir/paritaprevir/ritonavir.
		↔ S-Methadone	0.99 (0.91-1.08)	0.99 (0.89-1.09)	0.86 (0.76-0.96)	
		↔ ombitasvir/paritaprevir and dasabuvir (based on the cross-study comparison)				
buprenorphine/ naloxone 4-24 mg/1-6 mg once daily[8] Mechanism: CYP3A4 inhibition by ritonavir and UGT inhibition by paritaprevir, ombitasvir and dasabuvir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	↑ 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 dasabuvir + ombitasvir/paritaprevir/ritonavir.
		↑ norbu-prenorphine	2.07 (1.42-3.01)	1.84 (1.30-2.60)	2.10 (1.49- 2.97)	
		↑ naloxone	1.18 (0.81-1.73)	1.28 (0.92-1.79)	NA	
		↔ ombitasvir /paritaprevir and dasabuvir (based on the cross-study comparison)				
MUSCLE RELAXANTS						
Carisoprodol 250 mg single dose Mechanism: CYP2C19 induction by ritonavir	dasabuvir + ombitasvir/paritaprevir/ritonavir	↓ Carisoprodol	0.54 (0.47-0.63)	0.62 (0.55-0.70)	NA	No dose adjustment required for carisoprodol; increase dose if clinically indicated.
		↔ dasabuvir	0.96 (0.91-1.01)	1.02 (0.97-1.07)	1.00 (0.92-1.10)	
		↔ ombitasvir	0.98 (0.92-1.04)	0.95 (0.92-0.97)	0.96 (0.92-0.99)	
		↔ paritaprevir	0.88 (0.75-1.03)	0.96 (0.85-1.08)	1.14 (1.02-1.27)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Cyclobenzaprine 5 mg single dose Mechanism: decrease possibly due to CYP1A2 induction by ritonavir	dasabuvir + ombitasvir/paritaprevir/ritonavir	↓ cyclobenzaprine	0.68 (0.61-0.75)	0.60 (0.53-0.68)	NA	No dose adjustment for cyclobenzaprine required; increase dose if clinically indicated.
		↔ dasabuvir	0.98 (0.90-1.07)	1.01 (0.96-1.06)	1.13 (1.07-1.18)	
		↔ ombitasvir	0.98 (0.92-1.04)	1.00 (0.97-1.03)	1.01 (0.98-1.04)	
		↔ paritaprevir	1.14 (0.99-1.32)	1.13 (1.00-1.28)	1.13 (1.01-1.25)	
NARCOTIC ANALGESICS						
Paracetamol (given as fixed dose hydrocodone /paracetamol) 300 mg single dose	dasabuvir + ombitasvir/paritaprevir/ritonavir	↔ Paracetamol	1.02 (0.89-1.18)	1.17 (1.09-1.26)	NA	No dose adjustment is necessary for paracetamol when administered with dasabuvir + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	1.13 (1.01-1.26)	1.12 (1.05-1.19)	1.16 (1.08-1.25)	
		↔ ombitasvir	1.01 (0.93-1.10)	0.97 (0.93-1.02)	0.93 (0.90-0.97)	
		↔ paritaprevir	1.01 (0.80-1.27)	1.03 (0.89-1.18)	1.10 (0.97-1.26)	
Hydrocodone (as given in a fixed-dose hydrocodone /paracetamol) 5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir	dasabuvir + ombitasvir/paritaprevir/ritonavir	↑ hydrocodone	1.27 (1.14-1.40)	1.90 (1.72-2.10)	NA	A reduction of hydrocodone dose by 50% and/or clinical monitoring should be considered when administered with dasabuvir + ombitasvir/paritaprevir/ritonavir.
		Changes for dasabuvir and ombitasvir, paritaprevir are the same as shown for paracetamol above				
PROTON PUMP INHIBITORS						
Omeprazole 40 mg once daily Mechanism: CYP2C19 induction by ritonavir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	↓ omeprazole	0.62 (0.48-0.80)	0.62 (0.51-0.75)	NA	If clinically indicated, higher doses of omeprazole should be used. No dose adjustment needed for dasabuvir + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	1.13 (1.03-1.25)	1.08 (0.98-1.20)	1.05 (0.93-1.19)	
		↔ ombitasvir	1.02 (0.95-1.09)	1.05 (0.98-1.12)	1.04 (0.98-1.11)	
		↔ paritaprevir	1.19 (1.04-1.36)	1.18 (1.03-1.37)	0.92 (0.76-1.12)	

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Esomeprazole Lansoprazole Mechanism: CYP2C19 induction by ritonavir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not studied. Expected: ↓ esomeprazole, lansoprazole				If clinically indicated, higher doses of esomeprazole/lansoprazole may be needed.
SEDATIVES / HYPNOTICS						
Zolpidem 5 mg single dose	dasabuvir + ombitasvir/paritaprevir/ritonavir	↔ zolpidem	0.94 (0.76-1.16)	0.95 (0.74-1.23)	NA	No dose adjustment is necessary for zolpidem. No dose adjustment needed for dasabuvir + ombitasvir/paritaprevir/ritonavir.
		↔ dasabuvir	0.93 (0.84-1.03)	0.95 (0.84-1.08)	0.92 (0.83-1.01)	
		↔ ombitasvir	1.07 (1.00-1.15)	1.03 (1.00-1.07)	1.04 (1.00-1.08)	
		↓ paritaprevir	0.63 (0.46-0.86)	0.68 (0.55-0.85)	1.23 (1.10-1.38)	
Diazepam 2 mg single dose Mechanism: CYP2C19 induction by ritonavir	dasabuvir + ombitasvir/paritaprevir/ritonavir	↓diazepam	1.18 (1.07-1.30)	0.78 (0.73-0.82)	NA	No dose adjustment required for diazepam; increase dose if clinically indicated.
		↓ nordiazepam	1.10 (1.03-1.19)	0.56 (0.45-0.70)	NA	
		↔ dasabuvir	1.05 (0.98-1.13)	1.01 (0.94-1.08)	1.05 (0.98-1.12)	
		↔ ombitasvir	1.00 (0.93-1.08)	0.98 (0.93-1.03)	0.93 (0.88-0.98)	
		↔ paritaprevir	0.95 (0.77-1.18)	0.91 (0.78-1.07)	0.92 (0.82-1.03)	
Alprazolam 0.5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir.	dasabuvir + 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 dasabuvir + 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						

Medicinal Product/ Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{trough}	Clinical Comments
Levothyroxine Mechanism: UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	dasabuvir + ombitasvir/paritaprevir/ritonavir	Not studied. Expected: ↑ levothyroxine				Clinical monitoring and dose adjustment may be required for levothyroxine.

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 dasabuvir + 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 dasabuvir + ombitasvir/paritaprevir/ritonavir.
3. Ciclosporin 100 mg dosed alone and 30 mg administered with dasabuvir + ombitasvir/paritaprevir/ritonavir. Dose normalized cyclosporine ratios are shown for interaction with dasabuvir + ombitasvir/paritaprevir/ritonavir.
4. C_{12}:= concentration at 12 hours following single dose of everolimus.
5. Sirolimus 2 mg was dosed alone, 0.5 mg administered with dasabuvir + ombitasvir/paritaprevir/ritonavir. Dose normalized sirolimus ratios are shown for interaction with ombitasvir/paritaprevir/ritonavir + dasabuvir.
6. C_{24}:= concentration at 24 hours following single dose of cyclosporine, tacrolimus or sirolimus.
7. Tacrolimus 2 mg was dosed alone and 2 mg was administered with dasabuvir + ombitasvir/paritaprevir/ritonavir. Dose normalized tacrolimus ratios are shown for interaction with dasabuvir + ombitasvir/paritaprevir/ritonavir.
8. Dose normalised parameters reported for methadone, buprenorphine and naloxone.

Note: Doses used for dasabuvir + 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. dasabuvir + ombitasvir/paritaprevir/ritonavir was administered as multiple doses in all the drug interaction studies except the drug interaction studies with carbamazepine, gemfibrozil, ketoconazole, and sulfamethoxazole/trimethoprim.

Paediatric population

Drug interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential /contraception in males and females

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients when dasabuvir is used with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Refer to the Summary of Product Characteristics for ribavirin for additional information.

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

Male patients and their female partners: Either male patients or their female partners of childbearing potential must use a form of effective contraception during treatment with ribavirin and for 7 months after treatment.

Ethinyloestradiol is contraindicated in combination with dasabuvir (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 dasabuvir 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 dasabuvir during pregnancy.

If ribavirin is co-administered with dasabuvir 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 dasabuvir, 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

Dasabuvir has no or negligible influence on the ability to drive and use machines. Patients should be informed that fatigue has been reported during treatment with dasabuvir in combination with ombitasvir/paritaprevir/ritonavir and ribavirin (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In subjects receiving dasabuvir and ombitasvir/paritaprevir/ritonavir with ribavirin, the most commonly reported adverse reactions (greater than 20% of subjects) were fatigue and nausea. The

proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.2% (5/2,044) and 4.8% (99/2,044) of subjects had ribavirin dose reductions due to adverse reactions.

Tabulated list of adverse reactions

The safety summary is based on pooled data from phase 2 and 3 clinical trials in subjects who received dasabuvir and ombitasvir/paritaprevir/ritonavir with or without ribavirin. The majority of adverse reactions presented in Table 3 were of grade 1 severity in dasabuvir- 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 dasabuvir in combination with ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir and ribavirin

Frequency	**dasabuvir and ombitasvir/paritaprevir/ritonavir + ribavirin* N = 2,044**	**dasabuvir and ombitasvir/paritaprevir/ritonavir N = 588**
Blood and lymphatic system disorders		
Common	Anaemia	
Immune system disorders		
Frequency unknown	Anaphylactic reactions	Anaphylactic reactions
Metabolism and nutrition disorders		
Uncommon	Dehydration	
Psychiatric disorders		
Very common	Insomnia	
Gastrointestinal disorders		
Very common	Nausea, Diarrhoea	
Common	Vomiting	
Hepatobiliary disorders		
Frequency unknown	Hepatic decompensation and hepatic failure	Hepatic decompensation and hepatic failure
Skin and subcutaneous tissue disorders		
Very common	Pruritus	
Common		Pruritus
Rare	Angioedema	Angioedema
General disorders and administration and administration site conditions		
Very common	Asthenia Fatigue	

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

Description of selected adverse reactions

Compared to subjects without cirrhosis, in subjects with compensated cirrhosis there was an increased rate of indirect hyperbilirubinemia when ribavirin was part of the regimen.

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)
	dasabuvir and ombitasvir/paritaprevir /ritonavir + ribavirin 12 weeks N = 770 n (%)	dasabuvir and ombitasvir/paritaprevir /ritonavir 12 weeks N = 509 n (%)	dasabuvir 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 dasabuvir 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 ethinyloestradiol-containing medicine, such medicinal products are contraindicated with dasabuvir and ombitasvir/paritaprevir/ritonavir. No increase in incidence of ALT elevations was observed with other types of systemic oestrogens commonly used for hormone replacement therapy (e.g., oestradiol and conjugated oestrogens). 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 dasabuvir and ombitasvir/paritaprevir/ritonavir due to elevated ALT, including one on ethinyloestradiol. Three interrupted dasabuvir and ombitasvir/paritaprevir/ritonavir for one to seven days, including one on ethinyloestradiol. The majority of these ALT elevations were transient and assessed as related to dasabuvir 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 dasabuvir 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 dasabuvir and ombitasvir/paritaprevir/ritonavir and ribavirin (in addition to their immunosuppressant medicinal products) was similar to subjects treated with dasabuvir 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.

GT1-infected subjects with or without cirrhosis with severe renal impairment or end-stage renal disease (ESRD)
Dasabuvir and ombitasvir/paritaprevir/ritonavir with or without ribavirin were assessed in 68 subjects with genotype 1 infection with or without cirrhosis who have severe renal impairment or ESRD (see Section 5.1). The overall safety profile in subjects with severe renal impairment was similar to that seen in prior Phase 3 studies in subjects without severe renal impairment, except that a greater proportion of subjects required intervention due to ribavirin-associated decreases in serum haemoglobin. The mean baseline haemoglobin level was 12.1 g/dL and the mean decline in haemoglobin at the end of treatment for subjects taking RBV was 1.2 g/dL. Thirty-nine of the 50 subjects who received ribavirin required interruption of ribavirin, and 11 of these subjects were also treated with erythropoietin. Four subjects experienced a haemoglobin level < 8 g/dL. Two subjects received a blood transfusion. Adverse events of anaemia were not seen in the 18 GT1b-infected subjects who did not receive ribavirin. Ombitasvir/paritaprevir/ritonavir with or without dasabuvir was also evaluated without ribavirin in 18 GT1a- and GT4-infected patients; no adverse events of anaemia were seen in these subjects.

Paediatric population

The safety of dasabuvir 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 national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome.

Co-administration of dasabuvir with ombitasvir/paritaprevir/ritonavir combines three direct-acting antiviral medicinal products 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 dasabuvir 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 dasabuvir 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 dasabuvir in combination with ombitasvir/paritaprevir/ritonavir with and without ribavirin was evaluated in eight Phase 3 clinical trials, including two trials exclusively in subjects with compensated cirrhosis (Child-Pugh A), in over 2,360 subjects with genotype 1 chronic hepatitis C infection as summarised in Table 6.

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

Trial	Number of subjects treated	HCV genotype (GT)	Summary of study design
Treatment-naïve, without cirrhosis			
SAPPHIRE I	631	GT1	Arm A: dasabuvir and ombitasvir/paritaprevir/ritonavir + RBV Arm B: Placebo
PEARL III	419	GT1b	Arm A: dasabuvir and ombitasvir/paritaprevir/ritonavir + RBV Arm B: dasabuvir and ombitasvir/paritaprevir/ritonavir
PEARL IV	305	GT1a	Arm A: dasabuvir and ombitasvir/paritaprevir/ritonavir + RBV Arm B: dasabuvir and ombitasvir/paritaprevir/ritonavir
GARNET (open-label)	166	GT1b	dasabuvir and ombitasvir/paritaprevir/ritonavir (8 weeks)
Peginteferon+ribavirin-experienced, without cirrhosis			
SAPPHIRE II	394	GT1	Arm A: dasabuvir and ombitasvir/paritaprevir/ritonavir + RBV Arm B: Placebo
PEARL II (open-label)	179	GT1b	Arm A: dasabuvir and ombitasvir/paritaprevir/ritonavir + RBV Arm B: dasabuvir and ombitasvir/paritaprevir/ritonavir
Treatment-naïve and peginterferon+ribavirin-experienced, with compensated cirrhosis			
TURQUOISE II (open-label)	380	GT1	Arm A: dasabuvir and ombitasvir/paritaprevir/ritonavir + RBV (12 weeks) Arm B: dasabuvir and ombitasvir/paritaprevir/ritonavir + RBV (24 weeks)
TURQUOISE III (open-label)	60	GT1b	dasabuvir and ombitasvir/paritaprevir/ritonavir (12 weeks)

In all eight trials, the dasabuvir dose was 250 mg twice daily and the ombitasvir/paritaprevir/ritonavir dose was 25 mg/150 mg/100 mg once daily. For subjects who received ribavirin, the ribavirin dose

was 1000 mg per day for subjects weighing less than 75 kg or 1200 mg per day for subjects weighing greater than or equal to 75 kg.

Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate in the Phase 3 studies and was defined as unquantifiable or undetectable HCV RNA 12 weeks after the end of treatment (SVR12). Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels (no response guided algorithm). Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System (except GARNET which used COBAS AmpliPrep/COBAS TaqMan HCV Test v2.0). The High Pure system assay had a lower limit of quantification (LLOQ) of 25 IU per mL and the AmpliPrep assay had a LLOQ of 15 IU per mL.

Clinical trials in treatment-naïve adults

SAPPHIRE-I – genotype 1, treatment-naïve, without cirrhosis

Design: randomised, global multicentre, double-blind, placebo-controlled
Treatment: dasabuvir and ombitasvir/paritaprevir/ritonavir with weight-based 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; 15.2% had a history of depression or bipolar disorder; 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. SVR12 for genotype 1-infected treatment-naïve subjects in SAPPHIRE-I

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

a. Confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Other includes early drug discontinuation not due to virologic failure and missing HCV RNA values in the SVR12 window.

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

PEARL-III – genotype 1b, treatment-naïve, without cirrhosis

Design: randomised, global multicentre, double-blind, regimen-controlled
Treatment: dasabuvir and ombitasvir/paritaprevir/ritonavir without ribavirin or with weight-based ribavirin for 12 weeks

Treated subjects (N=419) had a median age of 50 years (range: 19 to 70); 45.8% were male; 4.8% were Black; 9.3% had a history of depression or bipolar disorder; 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. SVR12 for genotype 1b-infected treatment-naïve subjects in PEARL III

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

PEARL-IV – genotype 1a, treatment-naïve, without cirrhosis

Design: randomised, global multicentre, double-blind, regimen-controlled
Treatment: dasabuvir and ombitasvir/paritaprevir/ritonavir without ribavirin or with weight-based ribavirin for 12 weeks

Treated subjects (N=305) had a median age of 54 years (range: 19 to 70); 65.2% were male; 11.8% were Black; 20.7% had a history of depression or bipolar disorder; 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. SVR12 for genotype 1a-infected treatment-naïve subjects in PEARL IV

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

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

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

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

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

	dasabuvir and ombitasvir/paritaprevir/ritonavir for 8 weeks n/N (%)
SVR_{12}	160/163 (98.2)
95% CI[a]	96.1, 100.0
F0-F1	138/139 (99.3)[b]
F2	9/9 (100)
F3	13/15 (86.7)[c]

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

Clinical trials in peginterferon+ribavirin-experienced adults

SAPPHIRE-II – genotype 1, pegIFN+RBV-experienced, without cirrhosis

Design: randomised, global multicentre, double-blind, placebo-controlled
Treatment: dasabuvir and ombitasvir/paritaprevir/ritonavir with weight-based 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; 20.6% had a history of depression or bipolar disorder; 87.1% had baseline HCV RNA levels of at least 800,000 IU per mL; 17.8% had portal fibrosis (F2) and 14.5% had bridging fibrosis (F3); 58.4% had HCV genotype 1a infection; 41.4% had HCV genotype 1b infection.

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

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

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

PEARL-II – genotype 1b, pegIFN+RBV-experienced, without cirrhosis

Design: randomised, global multicentre, open-label, regimen-controlled
Treatment: dasabuvir and ombitasvir/paritaprevir/ritonavir without ribavirin or with weight-based ribavirin for 12 weeks

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; ; 12.8% had a history of depression or bipolar disorder; 87.7% had baseline HCV RNA levels of at least 800,000 IU/mL; 17.9% had portal fibrosis (F2) and 14.0% had bridging fibrosis (F3).

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

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

Clinical trial in subjects with compensated cirrhosis

TURQUOISE-II – treatment-naïve or pegIFN + RBV-experienced with compensated cirrhosis

Design: randomised, global multicentre, open-label
Treatment: dasabuvir and ombitasvir/paritaprevir/ritonavir with weight-based ribavirin for 12 or 24 weeks

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; 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; 24.7% had a history of depression or bipolar disorder; 68.7% had HCV genotype 1a infection, 31.3% had HCV genotype 1b infection.

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

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

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

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

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

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

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

TURQUOISE-III: treatment-naïve or pegIFN + RBV-experienced with compensated cirrhosis

Design: global multicentre, open-label
Treatment: dasabuvir and ombitasvir/paritaprevir/ritonavir without ribavirin for 12 weeks

60 patients were randomized and treated, and 60/60 (100%) achieved SVR12. Main characteristics are shown below.

Table 15. Main demographics in TURQUOISE-III

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

Pooled analyses of clinical trials

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

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

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

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

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

+Other types of pegIFN/RBV failure include less well documented non-response, relapse/breakthrough or other pegIFN failure.

Impact of ribavirin dose adjustment on probability of SVR
In Phase 3 clinical trials, 91.5% of subjects did not require ribavirin dose adjustments during therapy. In the 8.5% of subjects who had ribavirin dose adjustments during therapy, the SVR rate (98.5%) was comparable to subjects who maintained their starting ribavirin dose throughout treatment.

TURQUOISE-I: treatment-naïve or pegIFN + RBV-experienced with HCV GT1 or GT4/HIV-1 co-infection, without cirrhosis or with compensated cirrhosis

Design: randomised, global multicentre, open-label
Treatment: ombitasvir/paritaprevir/ritonavir with or without dasabuvir coadminstered with or without weight-based ribavirin for 12 or 24 weeks

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, dolutegravir (Part 2 only), or darunavir (Part 1b and Part 2 GT4 only)-, co-administered with a backbone of tenofovir plus emtricitabine or lamivudine. Part 1 of the study was a Phase 2 pilot cohort consisting of 2 parts, Part 1a (63 subjects) and Part 1b (22 subjects). Part 2 was a Phase 3 cohort consisting of 233 subjects.

In Part 1a, all subjects received dasabuvir and ombitasvir/paritaprevir/ritonavir with ribavirin for 12 or 24 weeks. Treated subjects (N = 63) had a median age of 51 years (range: 31 to 69); 24% were Black; 19% had compensated cirrhosis; 67% were treatment-naïve; 33% had failed prior treatment with pegIFN/RBV; 89% had HCV genotype 1a infection.

In Part 1b, all subjects received dasabuvir and ombitasvir/paritaprevir/ritonavir with ribavirin for 12 weeks. Treated subjects (N = 22) had a median age of 54 years (range: 34 to 68); 41% were Black; 14% had compensated cirrhosis; 86% were HCV treatment-naïve; 14% had failed prior treatment with pegIFN/RBV; 68% had HCV genotype 1a infection.

In Part 2, subjects with HCV GT1 received dasabuvir and ombitasvir/paritaprevir/ritonavir with or without ribavirin for 12 or 24 weeks. Subjects with HCV GT4 received ombitasvir/paritaprevir/ritonavir with ribavirin for 12 or 24 Weeks. Treated subjects (N = 233) had a median age of 49 years (range: 26 to 69); 10% were Black; 12% had compensated cirrhosis; 66% were treatment-naïve; 32% had failed prior treatment with pegIFN/RBV; 2% had failed prior treatment with sofosbuvir.

Table 17 shows the primary efficacy analysis of SVR12 performed on subjects with HCV GT1/HIV-1 co-infection that received recommended regimen in Part 2 of the TURQUOISE-I study.

Table 17. Primary SVR12 Assessment for Part 2, Subjects with HCV GT1/HIV-1 co-infection in TURQUOISE-I

Endpoint	**dasabuvir and ombitasvir/paritaprevir/ritonavir with or without ribavirin for 12 or 24 Weeks N = 200[a]**
SVR12, n/N (%) [95% CI]	194/200 (97.0) [93.6, 98.6]
Outcome for subjects not achieving SVR12	
On-treatment virologic failure	1
Post-treatment relapse	1
Other[b]	4

a. Includes all HCV GT1 subjects in Part 2 excluding Arm G subjects that did not receive recommended regimen.
b. Includes subjects who discontinued due to adverse event, lost to follow-up or subject withdrawal, and subjects with reinfection

Efficacy analyses performed on other parts of the study demonstrated similarly high SVR12 rates. In Part 1a, SVR12 was achieved by 29/31 (93.5%) subjects on the 12-week arm (95% CI: 79.3% – 98.2%) and by 29/32 (90.6%) subjects on the 24-week arm (95% CI: 75.8% – 96.8%). There was 1 relapse in the 12-week arm and 1 on-treatment virologic failure in the 24-week arm. In Part 1b, SVR12 was achieved by 22/22 (100%) subjects (95% CI: 85.1%, 100%). In Part 2, SVR12 was achieved by 27/28 (96.4%) subjects with HCV GT4/HIV-1 coinfection (95% CI: 82.3%, 99.4%) with no virologic failures.

The SVR12 rates in HCV/HIV-1 co-infected subjects were thus consistent with SVR12 rates in the phase 3 trials of HCV mono-infected subjects.
CORAL-I: treatment-naïve or pegIFN + RBV-experienced, GT 1 or GT4 infected, at least 3 months post liver transplant or 12 months post renal transplant

Design: randomised, global multicentre, open-label
Treatment: dasabuvir and ombitasvir/paritaprevir/ritonavir for 12 or 24 weeks with or without ribavirin (investigator chosen dose) for GT1 and GT4 infection

In subjects with liver transplant, no cirrhosis and GT1 infection, patients were dosed with dasabuvir and ombitasvir/paritaprevir/ritonavir for 12-24 weeks, with and without RBV. Liver transplant subjects with cirrhosis were dosed with dasabuvir and ombitasvir/paritaprevir/ritonavir with RBV (GT1a for 24 weeks [n=4], GT1b for 12 weeks [n=2]). Subjects with renal transplant and no cirrhosis were dosed for 12 weeks (with RBV for GT1a [n=9], without RBV for GT1b [n=3]). Subjects with liver transplant and GT4 infection were dosed with ombitasvir/paritaprevir/ritonavir with RBV (non-cirrhotic for 12 weeks [n=2] and cirrhotic for 24 weeks [n=1]. The dose of ribavirin was individualized at the discretion of the investigator, with most subjects receiving 600 to 800 mg as a starting dose, and most subjects also receiving 600 to 800 mg per day at the end of treatment.

A total of 129 subjects were treated, 84 with GT1a, 41 with GT1b, 1 with GT1 other, 3 with GT4 infection. Overall, 61% had fibrosis stage F0-F1, 26% F2, 9% F3, and 4% F4. 61% had prior HCV treatment experience before transplant. For immunosuppressive medication, most subjects were taking tacrolimus (81%), with the remainder taking cyclosporine.

Among all GT1 subjects who were post liver transplant, 111/114 (97.4%) achieved SVR12; with 2 relapsing post treatment and 1 breakthrough on treatment. Among the GT1 subjects who were post renal transplant, 9/12 (75%) achieved SVR12; however, there were no virologic failures. All 3 (100%) subjects with GT 4 infection who were post liver transplant achieved SVR12

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 dasabuvir 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; 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.

RUBY-I; treatment-naïve or pegIFN + RBV experienced with or without cirrhosis who have severe renal impairment or end stage renal disease (ESRD)

Design:	multicentre, open-label
Treatment:	dasabuvir and ombitasvir/paritaprevir/ritonavir with or without RBV for 12 or 24 weeks

Severe renal impairment or ESRD includes CKD Stage 4 defined as eGFR <30-15 mL/min/1.73 m^2 or CKD Stage 5 defined as <15 mL/min/1.73 m^2 or requiring haemodialysis. Treated subjects (N=68) had a median age of 58 years (range: 32-77 years); 83.8% were male; 58.8% were Black; 73.5% of subjects were infected with HCV GT1a; 75.0%% had Stage 5 CKD and 69.1% were on haemodialysis.

Sixty four of 68 (94.1%) subjects achieved SVR12. One subject experienced relapse at Post-Treatment Week 4, 2 subjects prematurely discontinued study drug and 1 subject had missing SVR12 data.

See also Section 4.8 for discussion of safety information for RUBY-I.

In another open-label phase 3b study evaluating 12 weeks of ombitasvir/paritaprevir/ritonavir with or without dasabuvir and without RBV in non-cirrhotic, treatment-naive GT1a and GT4 patients with CKD stage 4 or 5 (Ruby II), the SVR12 rate was 94.4% (17/18), with no subjects experiencing on-treatment virologic failure or relapse.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with dasabuvir 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 dasabuvir with ombitasvir/paritaprevir/ritonavir have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Table 18 shows mean C_{max} and AUC of dasabuvir 250 mg twice daily with ombitasvir/paritaprevir/ritonavir 25 mg/150 mg/100 mg once daily following multiple doses with food in healthy volunteers.

Table 18. Geometric mean C_{max}, AUC of multiple doses of dasabuvir 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, dasabuvir 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, dasabuvir 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. Limited data in patients with end-stage renal disease indicate no clinically significant changes in exposure also in this patient group. No dose adjustment of dasabuvir is required for patients with mild, moderate, or severe renal impairment, or end-stage-renal disease on dialysis (see section 4.2).

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

In subjects with mild, moderate and severe hepatic impairment, dasabuvir AUC values were 17% higher, 16% lower and 325% higher, respectively. The AUC values of dasabuvir M1 metabolite were unchanged, 57% lower, and 77% higher, respectively. Plasma protein binding of dasabuvir and its M1

metabolite were not meaningfully different in subjects with hepatic impairment compared to normal control subjects (see sections 4.2, 4.4 and 4.8).

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

5.3 Preclinical safety data

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

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

Similarly, dasabuvir was not carcinogenic in a 2-year rat study up to the highest dose tested (800 mg/kg/day), resulting in dasabuvir exposures approximately 19-fold higher than those in humans at 500 mg.

Dasabuvir had no effects on embryo-foetal viability or on fertility in rodents and were not teratogenic in two species. No adverse effects on behaviour, reproduction or development of offspring were reported. The highest dasabuvir dose tested produced exposures equal to 16 to 24-fold (rat) or 6-fold (rabbit) the exposures in humans at the maximum recommended clinical dose.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E 460(i))
Lactose monohydrate
Copovidone
Croscarmellose sodium
Colloidal anhydrous silica (E 551)
Magnesium stearate (E 470b)

Film-coating

Poly(vinyl alcohol) (E 1203)
Titanium dioxide (E 171)
Macrogol (3350)
Talc (E 553b)
Iron oxide yellow (E 172)
Iron oxide red (E 172)
Iron oxide black (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PCTFE aluminium foil blister packs.

Pack-size of 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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

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
Date of latest renewal: 26 September 2019

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton of multipack containing 56 (4 packs of 14) film-coated tablets - including blue box

1. NAME OF THE MEDICINAL PRODUCT

Exviera 250 mg film-coated tablets
dasabuvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 56 (4 packs of 14) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Take **one** tablet in the morning.
Take **one** tablet in the evening.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/983/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

exviera

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Inner carton of multipack of 14 film-coated tablets – without blue box

1. NAME OF THE MEDICINAL PRODUCT

Exviera 250 mg film-coated tablets
dasabuvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Take **one** tablet in the morning.
Take **one** tablet in the evening.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/983/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

exviera

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Exviera 250 mg tablets
dasabuvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Exviera 250 mg film-coated tablets
dasabuvir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Exviera is and what it is used for
2. What you need to know before you take Exviera
3. How to take Exviera
4. Possible side effects
5. How to store Exviera
6. Contents of the pack and other information

1. What Exviera is and what it is used for

Exviera contains the active substance dasabuvir. Exviera is an antiviral medicine used to treat adults with chronic (long-term) hepatitis C (an infectious disease that affects the liver, caused by the hepatitis C virus).

Exviera works by stopping the hepatitis C virus from multiplying and infecting new cells, thus clearing the virus from your blood over a period of time.

Exviera tablets do not work on their own. They are always taken with another antiviral medicine containing ombitasvir/paritaprevir/ritonavir. Some patients may also take an antiviral medicine called ribavirin. Your doctor will talk with you about which of these medicines to take with Exviera.

It is very important that you also read the package leaflets for the other antiviral medicines that you take with Exviera. If you have any questions about your medicines, please ask your doctor or pharmacist.

2. What you need to know before you take Exviera

Do not take Exviera:
- If you are allergic to dasabuvir or any of the other ingredients of this medicine (listed in section 6).
- If you have moderate to severe liver problems other than hepatitis C.
- If you are taking any of the medicines listed in the following table. This is because serious or life-threatening effects can occur when Exviera and ombitasvir/paritaprevir/ritonavir are taken with these medicines. These medicines can affect the way Exviera and ombitasvir/paritaprevir/ritonavir work and Exviera and ombitasvir/paritaprevir/ritonavir can affect the way these other medicines work.

Medicines you must not take with Exviera	
Medicine or active substance	**Purpose of the medicine**

carbamazepine, phenytoin, phenobarbital	for epilepsy
efavirenz, etravirine, nevirapine	for HIV infection
Apalutamide, enzalutamide	for prostate cancer
ethinyloestradiol containing medicines such as those contained in most contraceptive pills and vaginal rings used for contraception	for contraception
gemfibrozil	to lower cholesterol and other fats in the blood
mitotane	for some tumours of the adrenal glands
rifampicin	for bacterial infections
St. John's Wort (*hypericum perforatum*)	a herbal medicine for anxiety and mild depression. This medicine is available without a prescription

Do not take Exviera if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Exviera.

Warnings and precautions
Talk to your doctor or pharmacist before taking Exviera if you:
- have liver disease other than hepatitis C;
- have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely.
- have diabetes. You may need closer monitoring of your blood glucose levels and/or adjustment of your diabetes medicines after starting Exviera. Some diabetic patients have experienced low sugar levels in the blood (hypoglycaemia) after starting treatment with medicines like Exviera.

When taking Exviera and ombitasvir/paritaprevir/ritonavir, tell your doctor if you have the following symptoms as they may be a sign of worsening liver problems:
- Feel sick (nauseous), are sick (vomit) or lose your appetite.
- Notice yellowing of your skin or eyes.
- Your urine is darker than normal.
- Confusion
- Notice swelling of your stomach area

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Exviera.

Tell your doctor if you have a history of depression or psychiatric illness. Depression, including suicidal thoughts and behaviours, has been reported in some patients taking this medicine, particularly in patients with a prior history of depression or psychiatric illness or in patients taking ribavirin with this medicine. You or your caregiver should also immediately inform your doctor of any changes in behaviour or mood and of any suicidal thoughts you may have.

Blood tests
Your doctor will test your blood before, during and after your treatment with Exviera. This is so that your doctor can:
- Decide what other medicines you should take with Exviera and for how long.
- Confirm if your treatment has worked and if you are free of the hepatitis C virus.
- Check for side effects of Exviera or other antiviral medicines your doctor has prescribed for you to use with Exviera (such as "ombitasvir/paritaprevir/ritonavir" and "ribavirin").

Children and adolescents
Do not give Exviera to children and adolescents under 18 years of age. The use of Exviera in children and adolescents has not yet been studied.

Other medicines and Exviera
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

There are some medicines you **must not take** with Exviera - see the previous table "Medicines you must not take with Exviera".

Tell your doctor or pharmacist before taking Exviera, if you are taking any of the medicines in the table below. The doctor may need to change your dose of these medicines. Tell your doctor or pharmacist before taking Exviera if you are also using hormonal contraceptives. See the section on contraception below.

Medicines you must tell your doctor about before taking Exviera	
Medicine or active substance	**Purpose of the medicine**
alprazolam, diazepam	for anxiety, panic attacks and trouble sleeping
ciclosporin, everolimus, sirolimus, tacrolimus	to suppress the immune system
cyclobenzaprine, carisoprodol	for muscle spasms
dabigatran	to thin the blood
deferasirox	to help reduce iron levels in the blood
digoxin, amlodipine	for heart problems or high blood pressure
furosemide	for the build-up of too much fluid in the body
hydrocodone	for pain
imatinib	for the treatment of some cancers of the blood
levothyroxine	for thyroid problems
darunavir/ritonavir, atazanavir/ritonavir, rilpivirine	for HIV infection
omeprazole, lansoprazole, esomeprazole	for stomach ulcers and other stomach problems
rosuvastatin, pravastatin, fluvastatin, pitavastatin	to lower blood cholesterol
s-mephenytoin	for epilepsy
teriflunomide	for multiple sclerosis
sulfasalazine	to treat and manage inflammatory bowel disease or to treat rheumatoid arthritis
warfarin and other similar medicines called vitamin K antagonists*	to thin the blood

*Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Exviera.

Pregnancy and contraception

The effects of Exviera during pregnancy are not known. Exviera should not be used during pregnancy or in women of childbearing potential not using effective contraception.

- You or your partner must use an effective method of contraception during treatment. Contraceptive medicines that contains ethinyloestradiol cannot be used in combination with Exviera. Ask your doctor about the best contraception for you.

Extra precautions are needed if Exviera is taken together with ribavirin. Ribavirin may cause severe birth defects. Ribavirin stays for a long time in the body after treatment is stopped, and effective contraception is therefore needed both during treatment and for some time afterwards.

- There is a risk for birth defects when ribavirin is given to a female patient that becomes pregnant.
- There may also be a risk for birth defects if ribavirin is taken by a male patient, whose female partner becomes pregnant.
- Read the "Contraception" section of the package leaflet for ribavirin very carefully. It is important that both men and women read the information.
- If you or your partner becomes pregnant during treatment with Exviera and ribavirin or in the months that follow, you must contact your doctor immediately.

Breastfeeding
You should not breastfeed during treatment with Exviera. It is not known whether the active substance in Exviera (dasabuvir), passes into breast milk.

Driving and using machines
Some patients have reported feeling very tired when taking Exviera with other medicines for their hepatitis C infection. If you feel tired, do not drive or use any machines.

Exviera contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Exviera

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Exviera tablets do not work on their own. They are always taken with other antiviral medicines such as ombitasvir/paritaprevir/ritonavir. Your doctor may also give you an antiviral medicine called ribavirin.

How much to take
The recommended dose is one tablet, twice a day. Take one tablet in the morning and one tablet in the evening.

How to take
- Take the tablets with food. The type of food is not important.
- Swallow the tablets whole with water.
- Do not chew, crush or break the tablets as they may have a bitter taste.

How long to take Exviera for
You will take Exviera for 8, 12 or 24 weeks. Your doctor will tell you how long your treatment will last. Do not stop taking Exviera unless your doctor tells you to. It is very important that you complete the full course of treatment. This will give the medicines the best chance to clear the hepatitis C virus infection.

If you take more Exviera than you should
If you accidentally take more than the recommended dose, you should contact your doctor or go to the nearest hospital straight away. Keep the medicine pack with you so you can easily describe what you have taken.

If you forget to take Exviera
It is important not to miss a dose of this medicine. If you do miss a dose and it is:
- **More than 6 hours** until your next dose - take the missed dose with food as soon as possible.
- **Less than 6 hours** until your next dose - do not take the missed dose, take your next dose as usual with food.

Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Exviera and talk to your doctor or get medical help immediately if any of the following occur:

Side effects when taking Exviera with ombitasvir/paritaprevir/ritonavir with or without ribavirin:
Frequency not known: cannot be estimated based on available data
- Serious allergic reactions, signs may include:
  - Difficulty breathing or swallowing
  - Dizziness or light-headedness, which may be due to low blood pressure
  - Swelling of the face, lips, tongue or throat
  - Rash and itching of the skin
- Worsening liver problems. Symptoms include:
  - Feel sick (nauseous), are sick (vomit) or lose your appetite
  - Notice yellowing of your skin or eyes
  - Your urine is darker than normal
  - Confusion
  - Notice swelling of your stomach area

Tell your doctor or pharmacist if you notice any of the following side effects:

Side effects when taking Exviera with ombitasvir/paritaprevir/ritonavir:
Common: may affect up to 1 in 10 people
- Itching.

Rare: may affect up to 1 in 1,000 people
- Swelling of the layers of skin which can affect any part of the body including the face, tongue or throat and may cause difficulty swallowing or breathing (angioedema)

Side effects when taking Exviera and ombitasvir/paritaprevir/ritonavir with ribavirin:
Very common: may affect more than 1 in 10 people
- Feeling very tired (fatigue)
- Feeling sick (nausea)
- Itching
- Trouble sleeping (insomnia)
- Feeling weak or lack of energy (asthenia).
- Diarrhoea

Common: may affect up to 1 in 10 people
- Anaemia (low number of red blood cells).

- Vomiting

Uncommon: may affect up to 1 in 100 people
- Dehydration

Rare: may affect up to 1 in 1,000 people
- Swelling of the layers of skin which can affect any part of the body including the face, tongue or throat and may cause difficulty swallowing or breathing (angioedema)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Exviera

Keep this medicine out of the sight and reach of children.

Do not use the medicine after the expiry date which is stated on the carton after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Exviera contains
- Each tablet contains 250 mg of dasabuvir (as sodium monohydrate).
- The other ingredients are:
  - Tablet core: microcrystalline cellulose (E 460(i)), lactose monohydrate, copovidone, croscarmellose sodium, colloidal anhydrous silica (E 551), magnesium stearate (E 470b).
  - Tablet film-coating: poly(vinyl alcohol) (E 1203), titanium dioxide (E 171), macrogol (3350), talc (E 553b), iron oxide yellow (E 172), iron oxide red (E 172) and iron oxide black (E 172).

What Exviera looks like and contents of the pack
Exviera tablets are beige, ovaloid film-coated tablets, of dimensions of 14.0 mm x 8.0 mm, marked with "AV2". Exviera tablets are packed into foil blisters containing 2 tablets. Each carton contains 56 tablets (multipack carton containing 4 inner cartons of 14 tablets).

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.