ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Viekirax 12.5 mg/75 mg/50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pink, oblong, biconvex, film-coated tablets of dimensions 18.8 mm x 10.0 mm, debossed on one side with 'AV1'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Posology

The recommended oral dose of Viekirax is two 12.5 mg / 75 mg / 50 mg tablets once daily with food.

Viekirax should be used in combination with other medicinal products for the treatment of HCV (see Table 1).

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

Patient population	Treatment*	Duration
Genotype 1b, without cirrhosis	Viekirax + dasabuvir	12 weeks
Genotype 1b, with compensated cirrhosis	Viekirax + dasabuvir + ribavirin	12 weeks
Genotype 1a, without cirrhosis	Viekirax + dasabuvir + ribavirin*	12 weeks
Genotype 1a, with compensated cirrhosis	Viekirax + dasabuvir + ribavirin*	24 weeks (see section 5.1.)
Genotype 4, without cirrhosis	Viekirax + ribavirin	12 weeks
Genotype 4, with compensated cirrhosis	Viekirax + ribavirin	24 weeks
*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.		

For specific dosage instructions for dasabuvir and ribavirin, including dose modification, refer to the respective Summaries of Product Characteristics.

Missed doses
In case a dose of Viekirax is missed, the prescribed dose can be taken within 12 hours. If more than 12 hours have passed since Viekirax is usually taken, the missed dose should NOT be taken and the patient should take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

Special populations

HIV-1 Co-infection

Follow the dosing recommendations in Table 1. For dosing recommendations with HIV antiviral agents, refer to section 4.4 (Treatment of patients with HIV co-infection) and section 4.5. See section 5.1 for additional information.

Liver transplant recipients

Viekirax and dasabuvir in combination with ribavirin is recommended for 24 weeks in liver transplant recipients with genotype 1 HCV infection. Viekirax in combination with ribavirin is recommended in genotype 4 infection. 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 see section 4.5.

Elderly

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

Renal impairment

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

Hepatic impairment

No dose adjustment of Viekirax is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Viekirax have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B); however, no dose adjustment is expected to be required based on pharmacokinetic studies. Viekirax is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see sections 4.3 and 5.2).

Paediatric population

The safety and efficacy of Viekirax 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, Viekirax tablets should be taken with food, without regard to fat and calorie content (see section 5.2).

4.3 Contraindications

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

Patients with severe hepatic impairment (Child-Pugh C) (see section 5.2).

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

Medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious events must not be co-administered with Viekirax (see section 4.5). Examples are provided below.

CYP3A4 substrates:

- alfuzosin hydrochloride
- amiodarone
- astemizole, terfenadine
- cisapride
- colchicine in patients with renal or hepatic impairment
- ergotamine, dihydroergotamine, ergonovine, methylergometrine
- fusidic acid
- lovastatin, simvastatin, atorvastatin
- oral midazolam, triazolam
- pimozide
- quetiapine
- quinidine
- salmeterol
- sildenafil (when used for the treatment of pulmonary arterial hypertension)
- ticagrelor

Co-administration of Viekirax with or without dasabuvir with medicinal products that are strong or moderate enzyme inducers is expected to decrease ombitasvir, paritaprevir, and ritonavir plasma

concentrations and reduce their therapeutic effect and must not be co-administered (see section 4.5). Examples of contraindicated strong or moderate enzyme inducers are provided below.

Enzyme inducers:

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

Co-administration of Viekirax with or without dasabuvir with medicinal products that are strong inhibitors of CYP3A4 is expected to increase paritaprevir plasma concentrations and must not be co-administered with Viekirax (see section 4.5). Examples of contraindicated strong CYP3A4 inhibitors are provided below.

CYP3A4 inhibitors:

- cobicistat
- indinavir, lopinavir/ritonavir, saquinavir, tipranavir,
- itraconazole, ketoconazole, posaconazole, voriconazole
- clarithromycin, telithromycin
- conivaptan

4.4 Special warnings and precautions for use

General

Viekirax 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 sections 4.2 and 5.1).

Genotype-specific activity

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

The efficacy of Viekirax has not been established in patients with HCV genotypes 2, 3, 5 and 6; therefore Viekirax should not be used to treat patients infected with these genotypes.

There are no data on the use of Viekirax and ribavirin in patients with HCV genotype 4 infection with compensated cirrhosis and therefore the optimal treatment duration has not been established. Based on *in vitro* antiviral activity and available clinical data in HCV genotype 1, a conservative treatment duration of 24 weeks is recommended for patients with HCV genotype 4 and compensated cirrhosis.

Co-administration with other direct-acting antivirals against HCV

Viekirax safety and efficacy have been established in combination with dasabuvir and/or ribavirin. Co-administration of Viekirax with other antivirals has not been studied and therefore cannot be recommended.

Retreatment

The efficacy of Viekirax in patients previously exposed to Viekirax, or to medicinal products of the same classes as those of Viekirax (NS3/4A- or NS5A inhibitors), has not been demonstrated. Concerning cross-resistance, see also section 5.1.

Pregnancy and concomitant use with ribavirin

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

ALT elevations

During clinical trials with Viekirax and dasabuvir 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 Viekirax and dasabuvir with or without ribavirin.

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

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

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

Use with glucocorticoids metabolised by CYP3A (e.g. fluticasone)

Caution should be used when administering Viekirax with fluticasone or other glucocorticoids that are metabolised by CYP3A4. Concomitant use of inhaled glucocorticoids metabolised with CYP3A can increase systemic exposures of the glucocorticoids, and cases of Cushing's syndrome and subsequent adrenal suppression have been reported with ritonavir-containing regimens. Concomitant use of Viekirax and glucocorticoids, particularly long-term use, should only be initiated if the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.5).

Use with colchicine

The interaction between Viekirax with or without dasabuvir and colchicine has not been evaluated. A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with

normal renal or hepatic function if treatment with Viekirax with or without dasabuvir is required (see section 4.5). In patients with renal or hepatic impairment, use of colchicine with Viekirax with or without dasabuvir is contraindicated (see section 4.3 and 4.5).

Use with statins

Simvastatin, lovastatin and atorvastatin are contraindicated (see section 4.3 and 4.5).

Rosuvastatin
Viekirax with dasabuvir 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).The increase in rosuvastatin when combined with Viekirax without dasabuvir is less pronounced. In this combination, the maximum daily dose of rosuvastatin should be 10 mg (see section 4.5, Table 2).

Pitavastatin and fluvastatin
The interactions between pitavastatin and fluvastatin and Viekirax have not been investigated. Theoretically, Viekirax with and without dasabuvir is expected to increase the exposure to pitavastatin and fluvastatin. A temporary suspension of pitavastatin/fluvastatin is recommended for the duration of treatment with Viekirax. 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

Low dose ritonavir, which is part of the fixed dose combination Viekirax, 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 Viekirax.

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 Viekirax and dasabuvir, 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 Viekirax. 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 Viekirax and dasabuvir, 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 Viekirax.

HIV protease inhibitors other than atazanavir and darunavir (e.g., indinavir, saquinavir, tipranavir, lopinavir/ritonavir) are contraindicated (see section 4.3).

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 Viekirax and dasabuvir, with a consequent potential for QT-prolongation. If an HIV protease inhibitor is added (atazanavir, darunavir), rilpivirine exposure may increase even further and is therefore not recommended. Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring.

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

Hepatic impairment

No dose adjustment for Viekirax is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Viekirax have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B); however, no dose adjustment is expected to be required based on pharmacokinetic studies.
Viekirax is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see sections 4.3 and 5.2).

HCV/HBV (Hepatitis B Virus) co-infection

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

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

Viekirax may be administered with or without dasabuvir. 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 increase the risk of adverse events and ALT elevations (see Table 2). Coadministration with ethinylestradiol may increase the risk of ALT elevations (see sections 4.3 and 4.4). Examples of contraindicated enzyme inducers are provided in section 4.3.

Pharmacokinetic interactions

Potential for Viekirax 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 Viekirax with or without dasabuvir. See Table 2 for guidance regarding potential interactions with other medicinal products and dosing recommendations.

Medicinal products metabolised by CYP3A4
Ritonavir is a strong inhibitor of CYP3A. Co-administration of Viekirax with or without dasabuvir with medicinal products primarily metabolized by CYP3A may result in increased plasma concentrations of these medicinal products. Medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious events are contraindicated (see section 4.3 and Table 2).

CYP3A substrates evaluated in drug interaction studies which may require dose adjustment and/or clinical monitoring include (see Table 2) cyclosporine, tacrolimus, amlodipine, rilpivirine and alprazolam. Examples of other CYP3A4 substrates which may require dose adjustment and/or clinical monitoring include calcium channel blockers (e.g. nifedipine), and trazodone. Although buprenorphine and zolpidem are also metabolized by CYP3A, drug interaction studies indicate that no dose adjustment is needed when co-administering these medicinal products with Viekirax with or without dasabuvir (see Table 2).

Medicinal products transported by the OATP family and OCT1
Paritaprevir is an inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3, and paritaprevir and ritonavir are inhibitors of OATP2B1. Ritonavir is an *in vitro* inhibitor of OCT1, but the clinical relevance is unknown. Co-administration of Viekirax with or without dasabuvir with medicinal products that are substrates of OATP1B1, OATP1B3, OATP2B1 or OCT1 may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring. Such medicinal products include some statins (see Table 2), fexofenadine, repaglinide and angiotensin II receptor antagonists (e.g., valsartan).

OATP1B1/3 substrates evaluated in drug interaction studies include pravastatin and rosuvastatin (see Table 2).

Medicinal products transported by BCRP
Paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP *in vivo*. Co-administration of Viekirax with or without dasabuvir 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).

BCRP substrates evaluated in drug interaction studies include rosuvastatin (see Table 2).

Medicinal products transported by P-gp in the intestine
While paritaprevir, ritonavir and dasabuvir are *in vitro* inhibitors of P-gp, no significant change was observed in the exposure of the P-gp substrate digoxin when administered with Viekirax and dasabuvir. However, co-administration of digoxin with Viekirax without dasabuvir may result in increased plasma concentrations (see Table 2). Viekirax may increase the plasma exposure to medicinal products that are sensitive for changed intestinal P-gp activity (such as dabigatran etexilate).

Medicinal products metabolised by glucuronidation (UGT1A1)
Paritaprevir, ombitasvir and dasabuvir are inhibitors of UGT1A1. Co-administration of Viekirax with or without 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.

Medicinal products metabolised by CYP2C19
Co-administration of Viekirax with or without dasabuvir 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 (see Table 2).

Medicinal products metabolised by CYP2C9
Viekirax administered with or without dasabuvir 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
Viekirax administered with or without dasabuvir did not affect the exposures of the CYP2D6/CYP1A2 substrate, duloxetine. Other CYP1A2 substrates (e.g. ciprofloxacin, theophylline and caffeine) and CYP2D6 substrates (e.g. desipramine, metoprolol and dextromethorphan) are not expected to require dose adjustments.

Medicinal products renally excreted via transport proteins
Ombitasvir, paritaprevir, and ritonavir do not inhibit organic anion transporter (OAT1) *in vivo* as shown by the lack of interaction with tenofovir (OAT1 substrate). *In vitro* studies show that ombitasvir, paritaprevir, and ritonavir are not inhibitors of organic cation transporters (OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations.

Therefore, Viekirax with or without dasabuvir is not expected to affect medicinal products which are primarily excreted by the renal route via these transporters (see section 5.2).

Potential for other medicinal products to affect the pharmacokinetics of ombitasvir, paritaprevir, and dasabuvir

Medicinal products that inhibit CYP3A4
Co-administration of Viekirax with or without dasabuvir with strong inhibitors of CYP3A may increase paritaprevir concentrations (see section 4.3 and Table 2).

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

Medicinal products that inhibit CYP3A4 and transport proteins
Paritaprevir is eliminated via CYP3A4 mediated metabolism and biliary excretion (substrate of the hepatic transporters OATP1B1, P-gp and BCRP). Caution is advised if co-administering Viekirax with medicinal products that are both moderate inhibitors of CYP3A4 and inhibitors of multiple transporters (P-gp, BCRP and/or OATP1B1/ OATP1B3). These medicinal products may show clinically relevant increases in exposures of paritaprevir (e.g., ritonavir with atazanavir, erythromycin, diltiazem or verapamil).

Medicinal products that inhibit transport proteins
Potent inhibitors of P-gp, BCRP, OATP1B1 and/or OATP1B3 have the potential to increase the exposure to paritaprevir. Inhibition of these transporters is not expected to show clinically relevant increases in exposures of ombitasvir and dasabuvir.

Drug interaction studies

Recommendations for co-administration of Viekirax with and without dasabuvir 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 Viekirax with or without dasabuvir 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 Viekirax or Viekirax with dasabuvir, doses should be re-adjusted after administration of Viekirax or Viekirax with dasabuvir is completed.

Table 2 provides the Least Squares Means Ratio (90% Confidence Interval) effect on concentration of Viekirax with or without dasabuvir and concomitant medicinal products.

The magnitude of interaction when administered with medicinal products listed in Table 2 are similar (≤25% difference in the Least Square Means ratio) for Viekirax with or without dasabuvir, unless otherwise noted. Drug interactions were evaluated for the Viekirax and dasabuvir regimen, but not for the Viekirax without dasabuvir, with carbamazepine, furosemide, zolpidem, darunavir twice daily, darunavir (evening administration), atazanavir (evening administration) or rilpivirine. Thus, for these medicinal products, results and dosing recommendations of the Viekirax and dasabuvir regimen can be extrapolated to Viekirax without dasabuvir.

The direction of the arrow indicates the direction of the change in exposures (C_{max}, and AUC) in paritaprevir, ombitasvir, dasabuvir and the co-administered medicinal product (↑ = *increase (more than 20%),* ↓ = *decrease (of more than 20%),* ↔ = *no change* or change less than 20%). This is not an exclusive list.

Table 2. Interactions between Viekirax with or without dasabuvir and other medicinal products

Medicinal Product/Possible Mechanism of Interaction	**GIVEN WITH**	**EFFECT**	**C_{max}**	**AUC**	**C_{min}**	**Clinical Comments**
ALPHA 1-ADRENORECEPTOR ANTAGONIST						
Alfuzosin Mechanism: CYP3A inhibition by ritonavir	Viekirax with or without dasabuvir	Not studied. Expected ↑ alfuzosin				Concomitant use is contraindicated (see section 4.3).
AMINOSALICYLATE						
Sulfasalazine Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ sulfasalazine				Caution should be used when sulfasalazine is co-administered with Viekirax with or without dasabuvir. .
ANGIOTENSIN RECEPTOR BLOCKER						
Valsartan Mechanism: OATP1B inhibition by paritaprevir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ valsartan				Clinical monitoring and dose reduction is recommended when Viekirax with or without dasabuvir is coadministered with valsartan.
ANTIARRYTHMICS						
Digoxin 0.5 mg single dose Mechanism: P-gp	Viekirax + dasabuvir	↔ 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.
		↔ 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)	
		↔ dasabuvir	0.99 (0.92-1.07)	0.97 (0.91-1.02)	0.99 (0.92-1.07)	
	Viekirax	↑ digoxin	1.58	1.36	1.24	Decrease digoxin dose by

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
inhibition by paritaprevir, ritonavir and dasabuvir.	without dasabuvir		(1.43-1.73)	(1.21-1.54)	(1.07-1.43)	30-50%. Appropriate monitoring of serum digoxin levels is recommended.
		↔ ombitasvir r	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ paritaprevir				
Amiodarone Quinidine Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ amiodarone ↑ quinidine				Concomitant use is contraindicated (see section 4.3).
ANTIBIOTICS (SYSTEMIC ADMINISTRATION)						
Clarithromycin Telithromycin Mechanism: CYP3A4/P-gp inhibition by clarithromycin and ritonavir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ clarithromycin ↑ telithromycin ↑ paritaprevir ↑ dasabuvir				Concomitant use is contraindicated (see section 4.3)
Erythromycin Mechanism: CYP3A4/P-gp inhibition by erythromycin, paritaprevir, ritonavir and dasabuvir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ erythromycin ↑ paritaprevir ↑ dasabuvir				Administration of Viekirax with or without dasabuvir with erythromycin may result in increased concentrations of erythromycin and paritaprevir. Caution is advised.
Fusidic Acid Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ fusidic acid				Concomitant use is contraindicated (see section 4.3).
ANTICANCER AGENTS						
Enzalutamide Mitotane Mechanism: CYP3A4 induction enzalutamide or mitotane.	Viekirax with or without dasabuvir	Not studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contraindicated (see section 4.3).
Imatinib	Viekirax	Not Studied. Expected:				Clinical monitoring and

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.	with or without dasabuvir	↑ imatinib				lower doses of imatinib are recommended.
ANTICOAGULANTS						
Warfarin 5 mg single dose	Viekirax + dasabuvir	↔ R-warfarin	1.05 (0.95-1.17)	0.88 (0.81-0.95)	0.94 (0.84-1.05)	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalised ratio (INR) is recommended.
		↔ S-warfarin	0.96 (0.85-1.08)	0.88 (0.81-0.96)	0.95 (0.88-1.02)	
		↔ 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)	
		↔ dasabuvir	0.97 (0.89-1.06)	0.98 (0.91-1.06)	1.03 (0.94-1.13)	
	Viekirax without dasabuvir	↔ R-warfarin	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ S-warfarin				
		↔ paritaprevir				
		↔ ombitasvir				
Dabigatran etexilate Mechanism: Intestinal P-gp inhibition by paritaprevir and ritonavir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ dabigatran etexilate				Viekirax without dasabuvir may increase the plasma concentrations of dabigatran etexilate. Use with caution.
ANTICONVULSANTS						
Carbamazepine 200 mg once daily followed by 200 mg twice daily Mechanism:	Viekirax + dasabuvir	↔ 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)	
		↓ 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	
		↓ dasabuvir	0.45 (0.41-0.50)	0.30 (0.28-0.33)	NA	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
CYP3A4 induction by carbamazepine	Viekirax without dasabuvir	Not studied: similar effect expected as observed with Viekirax + dasabuvir.				
Phenobarbital Mechanism: CYP3A4 induction by phenobarbital.	Viekirax with or without dasabuvir	Not Studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contraindicated (see section 4.3).
Phenytoin Mechanism: CYP3A4 induction by phenytoin.	Viekirax with or without dasabuvir	Not Studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contraindicated (see section 4.3).
S-mephenytoin Mechanism: CYP2C19 induction by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↓ S-mephenytoin				Clinical monitoring and dose adjustment may be needed for s-mephenytoin.
ANTIDEPRESSANTS						
Escitalopram 10 mg single dose	Viekirax + dasabuvir	↔ 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	
		↔ 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)	
		↔ dasabuvir	1.10 (0.95-1.27)	1.01 (0.93-1.10)	0.89 (0.79-1.00)	
	Viekirax without dasabuvir	↓ es-citalopram	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ S-Desmethyl citalopram	1.17 (1.08-1.26)	1.07 (1.01-1.13)	NA	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔				

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
		paritaprevir				
Duloxetine 60 mg single dose	Viekirax + dasabuvir	↓ 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 Viekirax with or without dasabuvir.
		↔ 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)	
		↔ dasabuvir	0.94 (0.81-1.09)	0.92 (0.81-1.04)	0.88 (0.76-1.01)	
	Viekirax without dasabuvir	↔ duloxetine	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ paritaprevir	1.07 (0.63-1.81)	0.96 (0.70-1.32)	0.93 (0.76-1.14)	
Trazodone Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ trazodone				Trazodone should be used with caution and a lower dose of trazodone may be considered.
ANTI-DIURETIC HORMONE						
Conivaptan Mechanism: CYP3A4/P-gp inhibition by conivaptan and paritaprevir/ ritonavir/ombitasvir	Viekirax with or without dasabuvir	Not studied. Expected: ↑conivaptan ↑ paritaprevir ↑ dasabuvir				Concomitant use is contraindicated (see section 4.3)
ANTIFUNGALS						
Ketoconazole 400 mg once daily Mechanism: CYP3A4/P-gp inhibition by ketoconazole and paritaprevir/ ritonavir/ ombitasvir	Viekirax with dasabuvir	↑ keto-conazole	1.15 (1.09-1.21)	2.17 (2.05-2.29)	NA	Concomitant use is contraindicated (see section 4.3)
		↔ 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	
		↑ dasabuvir	1.16 (1.03-1.32)	1.42 (1.26-1.59)	NA	
	Viekirax without dasabuvir	↑ keto-conazole	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	1.72 (1.32-2.26)	2.16 (1.76-2.66)	NA	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Itraconazole Posaconazole Mechanism: CYP3A4 and/or P-gp inhibition by itraconazole, posaconazole and paritaprevir/ ritonavir/ombitasvir	Viekirax + dasabuvir	Not Studied. Expected: ↑ itraconazole ↑ posaconazole ↑ paritaprevir ↑ dasabuvir				Concomitant use is contraindicated (see section 4.3)
	Viekirax without dasabuvir					
Voriconazole Mechanism: CYP2C19 induction and CYP3A4 inhibition by ritonavir	Viekirax with or without dasabuvir	Not studied. Expected in CYP2C19 Extensive Metabolisers: ↓ voriconazole ↑ paritaprevir ↑ dasabuvir Not studied. Expected in CYP2C19 Poor Metabolisers: ↑ voriconazole ↑ dasabuvir ↑ paritaprevir				Concomitant use is contraindicated (see section 4.3).
ANTI-GOUT						
Colchicine Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ colchicine				A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with Viekirax with or without dasabuvir is required. Use of colchicine is contraindicated with Viekirax with or without dasabuvir in patients with renal or hepatic impairment (see sections 4.3 and 4.4)
ANTIHISTAMINES						
Astemizole	Viekirax	Not Studied. Expected:				Concomitant use is

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Terfenadine Mechanism: CYP3A4 inhibition by ritonavir.	with or without dasabuvir	↑ astemizole/terfenadine				contraindicated (see section 4.3).
Fexofenadine Mechanism: OATP1B1 inhibition by paritaprevir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ fexofenadine				Caution should be used when Viekirax with or without dasabuvir is coadministered with fexofenadine.
ANTIHYPERLIPIDAEMICS						
Gemfibrozil 600 mg twice daily Mechanism: Increase in dasabuvir exposure is possibly due to CYP2C8 inhibition and increase in paritaprevir possibly due to OATP1B1 inhibition by gemfibrozil.	Paritaprevir/ritonavir + dasabuvir	↑ paritaprevir	1.21 (0.94-1.57)	1.38 (1.18-1.61)	NA	Concomitant use of Viekirax with dasabuvir is contraindicated (see section 4.3).
		↑ dasabuvir	2.01 (1.71-2.38)	11.25 (9.05-13.99)	NA	
	Viekirax without dasabuvir	Not studied; No interaction expected when gemfibrozil is used in combination with Viekirax without dasabuvir.				No dose adjustment of gemfibrozil is necessary. No dose adjustment needed for Viekirax.
ANTIMYCOBACTERIALS						
Rifampicin Mechanism: CYP3A4 induction by rifampicin.	Viekirax with or without dasabuvir	Not Studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contraindicated (see section 4.3).
ANTIPSYCHOTICS						
Pimozide Quetiapine Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ pimozide,quetiapine				Concomitant use is contraindicated (see section 4.3).
ANTITPLATELET AGENTS						

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Ticagrelor Mechanism: CYP3A4 inhibition by ritonavir	Viekirax with or without dasabuvir	Not studied. Expected: ↑ ticagrelor				Concomitant use is contraindicated (see section 4.3).
CALCIUM CHANNEL BLOCKERS						
Amlodipine 5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax + dasabuvir	↑ amlodipine	1.26 (1.11-1.44)	2.57 (2.31-2.86)	NA	Decrease amlodipine dose by 50% and monitor patients for clinical effects.
		↔ ombitasvir	1.00 (0.95-1.06)	1.00 (0.97-1.04)	1.00 (0.97-1.04)	
		↓ paritaprevir	0.77 (0.64-0.94)	0.78 (0.68-0.88)	0.88 (0.80-0.95)	
		↔ dasabuvir	1.05 (0.97-1.14)	1.01 (0.96-1.06)	0.95 (0.89-1.01)	
	Viekirax without dasabuvir	Not studied: Similar effect expected as observed with Viekirax + dasabuvir.				
Diltiazem Verapamil Mechanism: CYP3A4/P-gp inhibition.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ diltiazem, verapamil ↑ paritaprevir ↑/↔ dasabuvir				Caution is advised due to the expected increase in paritaprevir exposures. Dose decrease and clinical monitoring of calcium channel blockers is recommended when co-administered with Viekirax with and without dasabuvir.
Nifedipine Mechanism: CYP3A4 inhibition	Viekirax with or without dasabuvir	Not studied. Expected: ↑ nifedipine				Dose decrease and clinical monitoring of calcium channel blockers is recommended when co-administered with Viekirax with and without dasabuvir.
CONTRACEPTIVES						
Ethinylestradiol/ norgestimate 0.035/0.25 mg once daily Mechanism: possibly due to UGT	Viekirax with or without dasabuvir	↔ ethinylestradiol	1.16 (0.90-1.50)	1.06 (0.96-1.17)	1.12 (0.94-1.33)	Ethinylestradiol-containing oral contraceptives are contraindicated (see section 4.3).
		Norgestimate metabolites:				
		↑ norgestrel	2.26 (1.91-2.67)	2.54 (2.09-3.09)	2.93 (2.39-3.57)	
		↑ nor-elgestromine	2.01 (1.77-2.29)	2.60 (2.30-2.95)	3.11 (2.51-3.85)	
		↔ ombitasvir	1.05 (0.81-1.35)	0.97 (0.81-1.15)	1.00 (0.88-1.12)	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
inhibition by paritaprevir, ombitasvir and dasabuvir.		↓ paritaprevir	0.70 (0.40-1.21)	0.66 (0.42-1.04)	0.87 (0.67-1.14)	
		↓ dasabuvir	0.51 (0.22-1.18)	0.48 (0.23-1.02)	0.53 (0.30-0.95)	
Nor-ethindrone (progestin only pill) 0.35 mg once daily	Viekirax + dasabuvir	↔ 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 Viekirax with or without dasabuvir.
		↔ 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)	
		↔ dasabuvir	1.01 (0.90-1.14)	0.96 (0.85-1.09)	0.95 (0.80-1.13)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
DIURETICS						
Furosemide 20 mg single dose Mechanism: possibly due to UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir.	Viekirax + dasabuvir	↑ furosemide	1.42 (1.17-1.72)	1.08 (1.00-1.17)	NA	Patients should be monitored for clinical effects; a decrease in furosemide dose of up to 50% may be required. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ 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)	
		↔ dasabuvir	1.12 (0.96-1.31)	1.09 (0.96-1.23)	1.06 (0.98-1.14)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
ERGOT ALKALOIDS						
Ergotamine Dihydroergotamine Ergonovine Methylergometrine Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ ergot derivatives				Concomitant use is contraindicated (see section 4.3).
GLUCOCORTICOIDS (INHALED)						
Fluticasone Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ fluticasone				Concomitant use of fluticasone can increase systemic exposures of fluticasone. Concomitant use of Viekirax and fluticasone particularly long-term use, should only

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
						be initiated if the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4).
GASTROINTESTINAL PRODUCTS (PROPULSIVE)						
Cisapride Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ cisapride				Concomitant use is contraindicated (see section 4.3).
HERBAL PRODUCTS						
St. John's Wort (*hypericum perforatum*) Mechanism: CYP3A4 induction by St. John's Wort	Viekirax with or without dasabuvir	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).						
Atazanavir 300 mg once daily (given at the same time) Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir.	Viekirax + dasabuvir	↔ 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 Viekirax with dasabuvir. Atazanavir must be administered at the same time as Viekirax with dasabuvir. Ritonavir dose in Viekirax will provide atazanavir pharmacokinetic enhancement). No dose adjustment needed for Viekirax with dasabuvir. Treatment with atazanavir + Viekirax without dasabuvir is not recommended-(↑ paritaprevir).
		↓ ombitasvir	0.77 (0.70-0.85)	0.83 (0.74-0.94)	0.89 (0.78-1.02)	
		↑ paritaprevir	1.46 (1.06-1.99)	1.94 (1.34-2.81)	3.26 (2.06-5.16)	
		↔ dasabuvir	0.83 (0.71-0.96)	0.82 (0.71-0.94)	0.79 (0.66-0.94)	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
						The combination of atazanavir and Viekirax + dasabuvir increase bilirubin levels, in particular when ribavirin is part of the hepatitis C regimen (see sections 4.4 and 4.8).
	Viekirax without dasabuvir	↔ atazanavir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	2.74 (1.76-4.27)	2.87 (2.08-3.97)	3.71 (2.87-4.79)	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
Atazanavir/ ritonavir 300/100 mg once daily (administered 12 hours apart) Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir and CYP3A by the additional dose of ritonavir.	Viekirax + dasabuvir	↔ atazanavir	1.02 (0.92-1.13)	1.19 (1.11-1.28)	1.68 (1.44-1.95)	
		↔ ombitasvir	0.83 (0.72-0.96)	0.90 (0.78-1.02)	1.00 (0.89-1.13)	
		↑ paritaprevir	2.19 (1.61-2.98)	3.16 (2.40-4.17)	11.95 (8.94-15.98)	
		↔ dasabuvir	0.81 (0.73-0.91)	0.81 (0.71-0.92)	0.80 (0.65-0.98)	
	Viekirax without dasabuvir	Not studied: Similar effect expected as observed with Viekirax + dasabuvir.				
Darunavir 800 mg once daily (given at the same time) Mechanism: Unknown	Viekirax + dasabuvir	↓ darunavir	0.92 (0.87-0.98)	0.76 (0.71-0.82)	0.52 (0.47-0.58)	The recommended dose of darunavir is 800 mg once daily, without ritonavir, when administered at the same time as Viekirax + dasabuvir (ritonavir dose in Viekirax will provide darunavir pharmacokinetic enhancement). This regimen can be used in the absence of extensive PI resistance (i.e. lack of
		↔ ombitasvir	0.86 (0.77-0.95)	0.86 (0.79-0.94)	0.87 (0.82-0.92)	
		↑ paritaprevir	1.54 (1.14-2.09)	1.29 (1.04-1.61)	1.30 (1.09-1.54)	
		↔ dasabuvir	1.10 (0.88-1.37)	0.94 (0.78-1.14)	0.90 (0.76-1.06)	
	Viekirax without dasabuvir	↔ darunavir	0.99 (0.92-1.08)	0. 92 (0.84-1.00)	0.74 (0.63-0.88)	
		↔	The magnitude of interaction was similar			

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
		ombitasvir	to that observed with Viekirax + dasabuvir.			darunavir associated RAMs), see also section 4.4. No dose adjustment needed for Viekirax with dasabuvir. Darunavir combined with Viekirax + dasabuvir is not recommended in patients with extensive PI resistance. Treatment with darunavir + Viekirax without dasabuvir is not recommended-(↑ paritaprevir).
		↑ paritaprevir	2.09 (1.35-3.24)	1.94 (1.36-2.75)	1.85 (1.41-2.42)	
Darunavir/ ritonavir 600/100 mg twice daily Mechanism: Unknown	Viekirax + dasabuvir	↔ darunavir	0.87 (0.79-0.96)	0.80 (0.74-0.86)	0.57 (0.48-0.67)	
		↓ 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)	
		↓ dasabuvir	0.84 (0.67-1.05)	0.73 (0.62-0.86)	0.54 (0.49-0.61)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
darunavir/ ritonavir 800/100 mg once daily (administered 12 hours apart) Mechanism: Unknown	Viekirax + dasabuvir	↑ darunavir	0.79 (0.70-0.90)	1.34 (1.25-1.43)	0.54 (0.48-0.62)	
		↔ 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)	
		↓ dasabuvir	0.75 (0.64-0.88)	0.72 (0.64-0.82)	0.65 (0.58-0.72)	
	Viekirax without dasabuvir	Not studied: Similar effect expected as observed with Viekirax + dasabuvir.				
Lopinavir / ritonavir	Viekirax + dasabuvir	↔ lopinavir	0.87 (0.76-0.99)	0.94 (0.81-1.10)	1.15 (0.93-1.42)	Concomitant use is contraindicated (see

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	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	1.14 (1.01-1.28)	1.17 (1.07-1.28)	1.24 (1.14-1.34)	section 4.3).
		↑ paritaprevir	2.04 (1.30-3.20)	2.17 (1.63-2.89)	2.36 (1.00-5.55)	
		↔ dasabuvir	0.99 (0.75-1.31)	0.93 (0.75-1.15)	0.68 (0.57-0.80)	
	Viekirax without dasabuvir	↔ lopinavir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	4.76 (3.54-6.39)	6.10 (4.30-8.67)	12.33 (7.30-20.84)	
Indinavir Saquinavir Tipranavir Mechanism: CYP3A4 inhibition by protease inhibitors.	Viekirax with or without dasabuvir	Not studied. Expected ↑ paritaprevir				Concomitant use is contraindicated (see section 4.3).
HIV ANTIVIRALS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS						
Rilpivirine[2] 25 mg once daily administered in the morning, with food \ Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax + dasabuvir	↑ rilpivirine	2.55 (2.08-3.12)	3.25 (2.80-3.77)	3.62 (3.12-4.21)	Co-administration of Viekirax with rilpivirine once daily should only be considered in patients without known QT-prolongation, and without other QT-prolongation co-medications. If the combination is used, repeated ECG-monitoring should be done, see section 4.4. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ 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)	
		↔ dasabuvir	1.18 (1.02-1.37)	1.17 (0.99-1.38)	1.10 (0.89-1.37)	
	Viekirax without dasabuvir	Not studied: Similar effect expected as observed with Viekirax + dasabuvir.				

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/300/200 mg once daily Mechanism: possible CYP3A4 induction by efavirenz.	Viekirax with or without dasabuvir	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 is contraindicated (see section 4.3).
Nevirapine etravirine	Viekirax with or without dasabuvir	Not Studied. Expected: ↓ ombitasvir ↓ paritaprevir ↓ dasabuvir				Concomitant use is contra-indicated (see section 4.3)
HIV ANTIVIRALS: INTEGRASE STRAND TRANSFER INHIBITOR						
Raltegravir 400 mg twice daily Mechanism: Increase in raltegravir exposures may be due to UGT1A1 inhibition by paritaprevir, ombitasvir. and dasabuvir	Viekirax + dasabuvir	↑ 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 Viekirax with or without dasabuvir.
		No clinically relevant changes in dasabuvir, paritaprevir and ombitasvir exposures (based on comparison with historical data) were observed during co-administration.				
	Viekirax without dasabuvir	↑ raltegravir	1.22 (0.78-1.89)	1.20 (0.74-1.95)	1.13 (0.51-2.51)	
		No clinically relevant changes in dasabuvir, paritaprevir and ombitasvir exposures (based on comparison with historical data) were observed during co-administration.				
HIV ANTIVIRALS: NUCLEOSIDE INHIBITORS						
Em-tricitabine/ tenofovir 200 mg once daily/300 mg once daily	Viekirax + dasabuvir	↔ 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 Viekirax with or without dasabuvir.
		↔ tenofovir	1.07 (0.93-1.24)	1.13 (1.07-1.20)	1.24 (1.13-1.36)	
		↔ 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)	
		↔ dasabuvir	0.85 (0.74-0.98)	0.85 (0.75-0.96)	0.85 (0.73-0.98)	
	Viekirax without	↔ em-tricitabine	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
	dasabuvir	↔ tenofovir	0.80 (0.71-0.90)	1.01 (0.96-1.07)	1.13 (1.06-1.21)	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ paritaprevir	1.02 (0.63-1.64)	1.04 (0.74-1.47)	1.09 (0.88-1.35)	
HIV ANTIVIRALS: PHARMACOKINETIC ENHANCER						
Cobicistat-containing regimens Mechanism: CYP3A4 inhibition by cobicistat	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ ombitasvir ↑ paritaprevir ↑ dasabuvir				Concomitant use is contraindicated (See section 4.3)
HMG CoA REDUCTASE INHIBITOR						
Rosuvastatin 5 mg once daily Mechanism: OATP1B inhibition by paritaprevir and BCRP inhibition by paritaprevir, ritonavir or dasabuvir.	Viekirax + dasabuvir	↑ 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 Viekirax with dasabuvir
		↔ 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)	
		↔ dasabuvir	1.07 (0.92-1.24)	1.08 (0.92-1.26)	1.15 (1.05-1.25)	
	Viekirax without dasabuvir	↑ rosuvastatin	2.61 (2.01-3.39)	1.33 (1.14-1.56)	0.65 (0.57-0.74)	The maximum daily dose of rosuvastatin should be 10 mg (see section 4.4). No dose adjustment needed for Viekirax.
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	1.40 (1.12-1.74)	1.22 (1.05-1.41)	1.06 (0.85-1.32)	
Pravastatin 10 mg once daily Mechanism: OATP1B1 inhibition by paritaprevir.	Viekirax+ dasabuvir	↑ pravastatin	1.37 (1.11-1.69)	1.82 (1.60-2.08)	NA	Reduce pravastatin dose by 50%. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	0.95 (0.89-1.02)	0.89 (0.83-0.95)	0.94 (0.89-0.99)	
		↔ dasabuvir	1.00 (0.87-1.14)	0.96 (0.85-1.09)	1.03 (0.91-1.15)	
		↔ paritaprevir	0.96 (0.69-1.32)	1.13 (0.92-1.38)	1.39 (1.21-1.59)	
	Viekirax without dasabuvir	↑ pravastatin	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	1.44 (1.15-1.81)	1.33 (1.09-1.62)	1.28 (0.83-1.96)	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
Fluvastatin Mechanism: OATP1B/BCRP inhibition by paritaprevir Pitavastatin Mechanism: OATP1B inhibition by paritaprevir	Viekirax with or without dasabuvir	Not studied. Expected: ↑ fluvastatin ↑ pitavastatin				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 with Viekirax. If statin treatment is required during the treatment period, a switch to dose reduced pravastatin or rosuvastatin is possible.
Lovastatin Simvastatin atorvastatin Mechanism: CYP3A4/OATP1B inhibition	Viekirax with or without dasabuvir	Not studied. Expected: ↑ lovastatin, simvastatin, atorvastatin				Concomitant use is contraindicated (see section 4.3).
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.	Viekirax + dasabuvir	↑ ciclosporin	1.01 (0.85-1.20)	5.82 (4.73-7.14)	15.8 (13.8-18.09)	When starting co-administration with Viekirax, give one fifth of the total daily dose of ciclosporin once daily with Viekirax. Monitor ciclosporin levels and adjust dose and/or dosing frequency as needed. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ 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)	
		↓ dasabuvir	0.66 (0.58-0.75)	0.70 (0.65-0.76)	0.76 (0.71-0.82)	
	Viekirax without dasabuvir	↑ ciclosporin	0.83 (0.72-0.94)	4.28 (3.66-5.01)	12.8 (10.6-15.6)	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↑ paritaprevir	1.39 (1.10-1.75)	1.46 (1.29-1.64)	1.18 (1.08-1.30)	
Tacrolimus	Viekirax +	↑ tacrolimus	3.99	57.1	16.6	When starting co-

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
2 mg single dose[4] Mechanism: Effect on tacrolimus is due to CYP3A4 inhibition by ritonavir.	dasabuvir		(3.21-4.97)	(45.5-71.7)	(13.0-21.2)	administration with Viekirax, administer 0.5 mg tacrolimus once every week. Monitor tacrolimus levels and adjust dose and/or dosing frequency as needed. No dose adjustment needed for Viekirax with or without dasabuvir.
		↔ ombitasvir	0.93 (0.88-0.99)	0.94 (0.89-0.98)	0.94 (0.91-0.96)	
		↓ paritaprevir	0.57 (0.42-0.78)	0.66 (0.54-0.81)	0.73 (0.66-0.80)	
		↔ dasabuvir	0.85 (0.73-0.98)	0.90 (0.80-1.02)	1.01 (0.91-1.11)	
	Viekirax without dasabuvir	↑ tacrolimus	4.27 (3.49-5.22)	85.8 (67.9-108)	24.6 (19.7-30.8)	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↓ paritaprevir				
INHALED BETA AGONISTS						
Salmeterol Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ salmeterol				Concomitant use is contraindicated (see section 4.3).
INSULIN SECRETAGOGUES						
Repaglinide Mechanism: OATP1B1 inhibition by paritaprevir.	Viekirax with or without dasabuvir	Not Studied. Expected: ↑ repaglinide				Caution should be used and dose decrease may be needed for repaglinide when administered with Viekirax with or without dasabuvir.
OPIOIDS						
Methadone 20-120 mg once daily[5]	Viekirax + dasabuvir	↔ 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 Viekirax with or without dasabuvir.
		↔ S-Methadone	0.99 (0.91-1.08)	0.99 (0.89-1.09)	0.86 (0.76-0.96)	
		↔ paritaprevir/ombitasvir/dasabuvir (based on the cross-study comparison)				
	Viekirax without dasabuvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.				
Buprenorphine	Viekirax + dasabuvir	↑ 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
		↑ norbu-	2.07	1.84	2.10	

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
/ naloxone 4-24 mg/1-6 mg once daily[5] Mechanism: CYP3A4 inhibition by ritonavir and UGT inhibition by paritaprevir, ombitasvir and dasabuvir.		prenorphine	(1.42-3.01)	(1.30-2.60)	(1.49-2.97)	and Viekirax with or without dasabuvir.
		↑ naloxone	1.18 (0.81-1.73)	1.28 (0.92-1.79)	NA	
		↔ ombitasvir/paritaprevir/dasabuvir (based on the cross-study comparison)				
	Viekirax without dasabuvir	↑ bu-prenorphine	1.19 (1.01-1.40)	1.51 (1.27-1.78)	1.65 (1.30-2.08)	
		↑ norbu-prenorphine	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ naloxone				
		↔ ombitasvir/paritaprevir (based on the cross-study comparison)				
PHOSPHODIESTERASE-(PDE-5) INHIBITORS						
Sildenafil (when used for treatment of pulmonary hypertension) Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with and without dasabuvir	Not studied. Expected: ↑ sildenafil				Concomitant use is contraindicated (see section 4.3).
PROTON PUMP INHIBITORS						
Omeprazole 40 mg once daily Mechanism: CYP2C19 induction by ritonavir.	Viekirax + dasabuvir	↓ 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 Viekirax with or without dasabuvir.
		↔ 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)	
		↔ dasabuvir	1.13 (1.03-1.25)	1.08 (0.98-1.20)	1.05 (0.93-1.19)	
	Viekirax without dasabuvir	↓ omeprazole	0.48 (0.29-0.78)	0.46 (0.27-0.77)	NA	
		↔ ombitasvir	The magnitude of interaction was similar to that observed with Viekirax + dasabuvir.			
		↔ paritaprevir				
Esomeprazole Lansoprazole Mechanism:	Viekirax with and without dasabuvir	Not studied. Expected: ↓ esomeprazole, lansoprazole				If clinically indicated, higher doses of esomeprazole/lansoprazole may be needed.

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
CYP2C19 induction by ritonavir.						
SEDATIVES / HYPNOTICS						
Zolpidem 5 mg single dose	Viekirax + dasabuvir	↔ 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 Viekirax with or without dasabuvir.
		↔ 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)	
		↔ dasabuvir	0.93 (0.84-1.03)	0.95 (0.84-1.08)	0.92 (0.83-1.01)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
Alprazolam 0.5 mg single dose Mechanism: CYP3A4 inhibition by ritonavir	Viekirax + dasabuvir	↑ 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 Viekirax with or without dasabuvir.
		↔ 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)	
		↔ dasabuvir	0.93 (0.83-1.04)	0.98 (0.87-1.11)	1.00 (0.87-1.15)	
	Viekirax without dasabuvir	Not studied. Similar effect expected as observed with Viekirax + dasabuvir.				
Oral midazolam Triazolam Mechanism: CYP3A4 inhibition by ritonavir.	Viekirax with or without dasabuvir	Not studied. Expected: ↑ midazolam or triazolam				Concomitant use is contraindicated (see section 4.3). If parenteral midazolam is co-administered with Viekirax with or without dasabuvir, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
THYROID HORMONES						
Levothyroxine Mechanism: UGT1A1 inhibition by paritaprevir,	Viekirax with or without dasabuvir	Not studied. Expected: ↑ levothyroxine				Clinical monitoring and dose adjustment may be required for levothyroxine

Medicinal Product/Possible Mechanism of Interaction	GIVEN WITH	EFFECT	C_{max}	AUC	C_{min}	Clinical Comments
ombitasvir and dasabuvir.						

1. Lopinavir/ritonavir 800/200 mg once daily (administered in the evening) was also administered with Viekirax with or without dasabuvir. 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 Viekirax with or without dasabuvir.

2. Rilpivirine was also administered in the evening with food and at night 4 hours after dinner with Viekirax + dasabuvir in other two arms in the study. The effect on rilpivirine exposures was similar to that observed when rilpivirine was administered in the morning with food with Viekirax + dasabuvir (shown in the table above).

3. Ciclosporin 100 mg dosed alone, 10 mg administered with Viekirax and 30 mg administered with Viekirax + dasabuvir. Dose normalized cyclosporine ratios are shown for interaction with Viekirax with or without dasabuvir.

4. Tacrolimus 2 mg was dosed alone and Tacrolimus 0.5 mg was administered with Viekirax and 2 mg was administered with Viekirax + dasabuvir. Dose normalized tacrolimus ratios are shown for interaction with Viekirax with or without dasabuvir.

5. Dose normalised parameters reported for methadone, buprenorphine and naloxone.

Note: Doses used for Viekirax and dasabuvir 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. Viekirax with or without dasabuvir was administered as multiple doses in all the drug interaction studies except the drug interaction studies with carbamazepine, gemfibrozil and ketoconazole.

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 Viekirax is taken in combination with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Women of childbearing potential and their male partners should not receive ribavirin unless they are using an effective form of contraception during treatment with ribavirin and for 6 months after treatment. Ethinylestradiol is contraindicated in combination with Viekirax (see sections 4.3 and 4.4).

Pregnancy

There are very limited data from the use of Viekirax in pregnant women. Studies with ombitasvir and paritaprevir/ritonavir in animals have shown malformations (see section 5.3). The potential risk for

humans is unknown. Viekirax should not be used during pregnancy or in women of childbearing potential not using effective contraception.

If ribavirin is co-administered with Viekirax, 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 paritaprevir /ritonavir or ombitasvir and their metabolites are excreted in human breast milk. Available pharmacokinetic data in animals have shown excretion of active substance and metabolite 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 breast-feeding or discontinue treatment with Viekirax, taking into account the importance of the therapy to the mother. For patients co-administered ribavirin refer to the Summary of Product Characteristics of ribavirin.

Fertility

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

4.7 Effects on ability to drive and use machines

Patients should be informed that fatigue has been reported during treatment with Viekirax in combination with dasabuvir and ribavirin (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

Viekirax and dasabuvir with ribavirin in subjects with genotype 1 hepatitis C infection (including subjects with compensated cirrhosis)

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

With the exception of increased rates of transient hyperbilirubinemia, the safety profile of Viekirax and dasabuvir with ribavirin in subjects with compensated cirrhosis was similar to that of subjects without cirrhosis.

Viekirax and dasabuvir without ribavirin in subjects with genotype 1 hepatitis C infection

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

Tabulated list of adverse reactions

Table 3 lists adverse reactions for which a causal relationship between paritaprevir/ombitasvir/ritonavir, in combination with dasabuvir and/or ribavirin, and the adverse event is at least a reasonable possibility. The

majority of adverse reactions presented in Table 3 were of grade 1 severity in Viekirax and dasabuvir-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 drug reactions identified with Viekirax in combination with dasabuvir with and without ribavirin

Frequency	**Viekirax + dasabuvir + ribavirin* N = 2,044**	**Viekirax + dasabuvir N = 588**
Blood and lymphatic system disorders		
Common	Anaemia	
Psychiatric disorders		
Very common	Insomnia	
Gastrointestinal disorders		
Very common	Nausea	
Skin and subcutaneous tissue disorders		
Very common	Pruritus	
Common		Pruritus
General disorders and administration and administration site conditions		
Very common	Asthenia Fatigue	

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

Description of selected adverse reactions

Laboratory abnormalities

Changes in selected laboratory parameters are described in Table 4. A side-by-side tabulation is shown to simplify presentation; direct comparison across trials should not be made due to differing 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)
	Viekirax and dasabuvir + ribavirin 12 weeks N = 770 n (%)	Viekirax and dasabuvir 12 weeks N = 509 n (%)	Viekirax and dasabuvir + 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 according to testing laboratory.			

Serum ALT elevations

In a pooled analysis of clinical trials with Viekirax and dasabuvir with and without ribavirin, 1% of subjects experienced serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. As the incidence of such elevations was 26% among women taking a concomitant ethinylestradiol-containing medicinal product, such medicinal products are contraindicated with Viekirax with or without dasabuvir. No increase in incidence of ALT elevations was observed with other types of estrogens commonly used for hormone replacement therapy (e.g. estradiol and conjugated estrogens). ALT elevations were typically asymptomatic, generally occurred during the first 4 weeks of treatment (mean time 20 days, range 8-57 days) and most resolved with ongoing therapy. Two patients discontinued Viekirax and dasabuvir due to elevated ALT, including one on ethinylestradiol. Three interrupted Viekirax and dasabuvir for one to seven days, including one on ethinylestradiol. The majority of these ALT elevations were transient and assessed as drug-related. 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 Viekirax and dasabuvir 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 Viekirax and dasabuvir and ribavirin (in addition to their immunosuppressant medications) was similar to subjects treated with Viekirax and dasabuvir and ribavirin in phase 3 clinical trials, although some adverse

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

HIV/HCV co-infected patients

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

Paediatric population

The safety of Viekirax 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 administered to healthy volunteers was 400 mg for paritaprevir (with 100 mg ritonavir), 200 mg for ritonavir (with 100 mg paritaprevir) and 350 mg for ombitasvir. No study related adverse reactions with paritaprevir, ritonavir, or ombitasvir were observed. Transient increases in indirect bilirubin were observed at the highest doses of paritaprevir/ritonavir. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; direct-acting antivirals, ATC code: not yet assigned

Mechanism of action

Viekirax, when co-administered with dasabuvir, combines three direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle. Refer to the Summary of Product Characteristics of dasabuvir for its pharmacological properties.

Ritonavir

Ritonavir is not active against HCV. Ritonavir is a CYP3A inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir.

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication.

Paritaprevir

Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.

Activity in cell culture and/or biochemical studies

Ombitasvir

The EC_{50} of ombitasvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays was 14.1 and 5 pM, respectively. The activity of ombitasvir was attenuated 11- to 13-fold in the presence of 40% human plasma. The mean EC_{50} of ombitasvir against replicons containing NS5A from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.66 pM (range 0.35 to 0.88 pM; n=11) and 1.0 pM (range 0.74 to 1.5 pM; n=11), respectively. Ombitasvir has EC_{50} values of 12, 4.3, 19, 1.7, 3.2, and 366 pM against replicon cell lines constructed with NS5A from single isolates representing genotypes 2a, 2b, 3a, 4a, 5a, and 6a, respectively.

Paritaprevir

The EC_{50} of paritaprevir against genotype 1a-H77 and 1b-Con1 strains in the HCV replicon cell culture assay was 1.0 and 0.21 nM, respectively. The activity of paritaprevir was attenuated 24 to 27 -fold in the presence of 40% human plasma. The mean EC_{50} of paritaprevir against replicons containing NS3 from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.86 nM (range 0.43 to 1.87 nM; n=11) and 0.06 nM (range 0.03 to 0.09 nM; n=9), respectively. Paritaprevir had an EC_{50} value of 5.3 nM against the 2a-JFH-1 replicon cell line, and EC_{50} values of 19, 0.09, and 0.68 nM against replicon cell lines containing NS3 from a single isolate each of genotype 3a, 4a, and 6a, respectively
Ritonavir did not exhibit a direct antiviral effect on the replication of HCV subgenomic replicons, and the presence of ritonavir did not affect the *in vitro* antiviral activity of paritaprevir.

Resistance

In cell culture

Genotype 1

Resistance to paritaprevir and ombitasvir conferred by variants in NS3 and NS5A respectively, 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 F43L, R155K, A156T, and D168A/F/H/V/Y in HCV NS3 reduced susceptibility to paritaprevir. In the genotype 1a replicon, the activity of paritaprevir was reduced 20-, 37-, and 17-fold by the F43L, R155K and A156T substitutions, respectively. The activity of paritaprevir was reduced 96-fold by D168V, and 50- to 219-fold by each of the other D168 substitutions. The activity of paritaprevir in genotype 1a was not significantly affected (less than or equal to 3-fold) by single substitutions V36A/M, V55I, Y56H, Q80K or E357K. Double variants including combinations of V36LM, F43L, Y56H, Q80K or E357K with R155K or with a D168 substitution reduced the activity of paritaprevir by an additional 2 to 3-fold relative to the single R155K or D168 substitution. In the genotype

1b replicon, the activity of paritaprevir was reduced 76- and 159-and 337- fold by D168A, D168H, D168V, and D168Y respectively. Y56H alone could not be evaluated due to poor replication capacity, however, the combination of Y56H and D168A/V/Y reduced the activity of paritaprevir by 700- to 4118-fold.

In genotype 1a, substitutions M28T/V, Q30E/R, L31V, H58D, Y93C/H/N, and M28V + Q30R in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1a replicon, the activity of ombitasvir was reduced by 896-, 58- and 243-fold against the M28T/V and H58D substitutions, respectively, and 1326-, 800-, 155-foldand 1675- to 66740- fold by the Q30E/R, L31V and Y93C/H/N substitutions, respectively. Y93H, Y93N or M28V in combination with Q30R reduced the activity of ombitasvir by more than 42,802-fold. In genotype 1b, substitutions L28T, L31F/V, as well as Y93H alone or in combination with L28M, R30Q, L31F/M/V or P58S in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1b replicon, the activity of ombitasvir was reduced by less than 10-fold by variants at amino acid positions 30 and 31. The activity of ombitasvir was reduced by 661-, 77-, 284- and 142-fold against the genotype 1b substitutions L28T, Y93H, R30Q in combination with Y93H, and L31M in combination with Y93H, respectively. All other double substitutions of Y93H in combination with substitutions at positions 28, 31, or 58 reduced the activity of ombitasvir by more than 400-fold.

Genotype 4

In genotype 4a, resistance to paritaprevir or ombitasvir by variants in NS3 or NS5A, respectively, selected in cell culture were phenotypically characterised. Substitutions R155C, A156T/V, and D168H/V in HCV NS3 reduced susceptibility to paritaprevir by 40- to 323-fold. Substitution L28V in HCV NS5A reduced the susceptibility to ombitasvir by 21-fold.

Effect of baseline HCV substitutions/polymorphisms on treatment outcome

A pooled analysis of subjects with genotype 1 HCV infection, who were treated with ombitasvir, paritaprevir, and dasabuvir (a non-nucleotide NS5B inhibitor) with or without ribavirin in the 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 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 ombitasvir, paritaprevir, and dasabuvir 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 Viekirax and dasabuvir 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 paritaprevir, ombitasvir, and dasabuvir resistance-associated amino acid substitutions in NS3, NS5A, and NS5B, respectively, was assessed in genotype 1a-infected subjects in Phase 2b trials. Paritaprevir treatment-emergent variants V36A/M, R155K or D168V were observed in NS3 in 47 subjects. Ombitasvir treatment-emergent variants M28T, M28V or Q30R in NS5A were observed in 32 subjects. Dasabuvir treatment-emergent variants M414T, G554S, S556G, G558R or D559G/N in NS5B were observed in 34 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 Viekirax- and dasabuvir-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 ombitasvir, paritaprevir or dasabuvir treatment experience on the efficacy of other NS5A inhibitors, NS3/4A protease inhibitors, or NS5B inhibitors has not been studied.

Clinical efficacy and safety

Clinical studies in subjects with genotype 1 hepatitis C infection

The efficacy and safety of Viekirax in combination with dasabuvir with and without ribavirin was evaluated in six randomised Phase 3 clinical trials, including one trial exclusively in subjects with cirrhosis (Child-Pugh A), in over 2,300 subjects with genotype 1 chronic hepatitis C infection as summarised in Table 6.

Table 6. Phase 3 randomised, global multicentre studies conducted with Viekirax and dasabuvir with or without ribavirin (RBV).

Trial[1]	Number of subjects treated[2]	HCV genotype (GT)	Summary of study design[3]
Treatment-naïve[4], without cirrhosis			
SAPPHIRE I	631	GT1	Arm A: Viekirax and dasabuvir + RBV Arm B: Placebo
PEARL III	419	GT1b	Arm A: Viekirax and dasabuvir + RBV Arm B: Viekirax and dasabuvir
PEARL IV	305	GT1a	Arm A: Viekirax and dasabuvir + RBV Arm B: Viekirax and dasabuvir
Peginterferon+ribavirin experienced-[5], without cirrhosis			
SAPPHIRE II	394	GT1	Arm A: Viekirax and dasabuvir + RBV Arm B: Placebo
PEARL II (open-label)	179	GT1b	Arm A: Viekirax and dasabuvir + RBV Arm B: Viekirax and dasabuvir
Treatment-naïve and peginterferon+ribavirin -experienced, with compensated cirrhosis			
TURQUOISE II (open-label)	380	GT1	Arm A: Viekirax and dasabuvir + RBV (12 weeks) Arm B: Viekirax and dasabuvir + RBV (24 weeks)

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

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

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

Clinical trials in treatment-naïve adults

SAPPHIRE-I – genotype 1, treatment-naïve

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

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

Table 7 shows the SVR12 rates for genotype 1-infected treatment-naïve subjects receiving Viekirax and dasabuvir in combination with ribavirin for 12 weeks in SAPPHIRE-I.

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

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

CI = confidence interval, VF = virologic failure

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

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

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

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

PEARL-III – genotype 1b, treatment-naïve

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

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

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

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

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

CI = confidence interval, VF = virologic failure

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

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

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

PEARL-IV – genotype 1a, treatment-naïve

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

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

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

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

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

CI = confidence interval, VF = virologic failure

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

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

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

Clinical trials in peginterferon+ribavirin-experienced adults

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

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

Treated subjects (N=394) had a median age of 54 years (range: 19 to 71); 49.0% were prior pegIFN/RBV null responders; 21.8/% were prior pegIFN/RBV partial responders, and 29.2% were prior pegIFN/RBV relapsers; 57.6% were male; 8.1% were Black; 19.8% had a body mass index of at least 30 kg/m^2; 20.6% had a history of depression or bipolar disorder; 89.6% had IL28B non-CC genotype; 87.1% had baseline HCV RNA levels of at least 800,000 IU per mL; 17.8% had portal fibrosis (F2) and 14.5% had bridging fibrosis (F3); 58.4% had HCV genotype 1a infection; 41.4% had HCV genotype 1b infection.

Table 10 shows the SVR12 rates for treatment-experienced subjects with genotype 1-infection receiving Viekirax and dasabuvir in combination with ribavirin for 12 weeks in SAPPHIRE-II.

Table 10. SVR12 for genotype 1-infected peginterferon+ribavirin-experienced subjects in SAPPHIRE-II

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

CI = confidence interval, VF = virologic failure

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

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

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

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

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

PEARL-II was a randomised, global multicentre, open-label trial conducted in 179 adults with chronic genotype 1b hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment pegIFN/RBV. Subjects were randomised in a 1:1 ratio to receive Viekirax and dasabuvir with or without ribavirin for 12 weeks of treatment.

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

Table 11 shows the SVR12 rates for genotype 1b-infected, peginterferon+ribavirin-experienced subjects who received Viekirax and dasabuvir with or without ribavirin for 12 weeks in PEARL II. In this study, Viekirax and dasabuvir without ribavirin had similar SVR12 rate (100%) compared to Viekirax and dasabuvir with ribavirin (97.7%).

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

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

CI = confidence interval, VF = virologic failure

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

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

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

Clinical trial in subjects with compensated cirrhosis

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

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

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

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

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

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

CI = confidence interval, VF = virologic failure

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

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

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

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

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

Table 13. TURQUOISE-II: Relapse Rates by Baseline Laboratory Values after 12 and 24 Weeks of Treatment in Subjects with Genotype 1a Infection and Compensated Cirrhosis

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

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

Pooled analyses of clinical trials

Durability of response

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

Pooled efficacy analysis

In Phase 3 clinical trials, 1083 subjects (including 189 with compensated cirrhosis) with genotype 1 HCV infection received the recommended regimen for their HCV genotype 1 subtype, cirrhosis status and relevant baseline characteristics. Table 14 shows SVR rates for these subjects.

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

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

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

Viekirax without ribavirin and without dasabuvir was also evaluated in genotype 1b infected subjects in Phase 2 studies M13-393 (PEARL-I) and M12-536. PEARL I was conducted in the US and Europe, M12-536 in Japan. The treatment-experienced subjects studied were primarily pegIFN+RBV null-responders. The doses of ombitasvir, paritaprevir, ritonavir were 25 mg 150 mg, 100 mg once daily in PEARL-I, while the dose of paritaprevir was 100 mg or 150 mg in study M12-536. Treatment duration was 12 weeks for treatment naïve subjects, 12-24 weeks for treatment experienced subjects and 24 weeks for subjects with cirrhosis. Overall, 107 of 113 subjects without cirrhosis and 147 of 155 subjects with cirrhosis achieved SVR12 after 12-24 weeks of treatment.

Viekirax with ribavirin & without dasabuvir was evaluated for 12 weeks in genotype 1 treatment naive and treatment experienced non-cirrhotic subjects in a phase 2 study M11-652 (AVIATOR). The doses of paritaprevir were 100 mg and 200 mg and ombitasvir 25 mg. Ribavirin was dosed based on weight (1000 mg – 1200 mg per day). Overall, 72 of 79 treatment-naive subjects (45 of 52 GT1a and 27 of 27 GT1b)

and 40 of 45 treatment-experienced subjects (21 of 26 GT1a and 19 of 19 GT1b) achieved SVR12 after 12 weeks of treatment.

Impact of ribavirin dose adjustment on probability of SVR

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

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

In an open-label clinical trial (TURQUOISE-I) the safety and efficacy of 12 or 24 weeks of treatment with Viekirax and dasabuvir and ribavirin was evaluated in 63 subjects with genotype 1 chronic hepatitis C co-infected with HIV-1. See section 4.2 for dosing recommendations in HCV/HIV-1 co-infected patients. Subjects were on a stable HIV-1 antiretroviral therapy (ART) regimen that included ritonavir-boosted atazanavir or raltegravir, co-administered with a backbone of tenofovir plus emtricitabine or lamivudine.

Treated subjects (N = 63) had a median age of 51 years (range: 31 to 69); 24% of subjects were Black; 81% of subjects had IL28B non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection.

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

Table 15. SVR12 for HIV-1 co-infected Subjects in TURQUOISE-I

Endpoint	Arm A 12 Weeks N = 31	Arm B 24 Weeks N = 32
SVR12, n/N (%) [95% CI]	29/31 (93.5) [79.3, 98.2]	29/32 (90.6) [75.8, 96.8]
Outcome for subjects not achieving SVR12		
On-treatment virologic failure[a]	0	1
Post-treatment relapse[b]	1	2[c]
Other[d]	1	0

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

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

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

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

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

Clinical Trial in liver transplant recipients with HCV genotype 1 infection

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

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

Clinical trial in patients receiving 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 +/- naloxone (N=19) received 12 weeks of Viekirax and dasabuvir with ribavirin. Treated subjects had a median age of 51 years (range: 26 to 64); 65.8% were male and 5.3% were Black. A majority (86.8%) had baseline HCV RNA levels of at least 800,000 IU/mL and a majority (84.2%) had genotype 1a infection; 68.4% had IL28B non-CC genotype; 15.8% had portal fibrosis (F2) and 5.3% had bridging fibrosis (F3); and 94.7% were naïve to prior HCV treatment.

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

Clinical trial in subjects with genotype 4 chronic hepatitis C

PEARL- I– genotype 4, treatment-naïve or peginterferon + ribavirin experienced

PEARL-I- was a randomised, global multicentre, open-label trial conducted in 135 adults with genotype 4 chronic hepatitis C virus infection without cirrhosis who were treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Treatment naive subjects were randomised in a 1:1 ratio to receive ombitasvir, paritaprevir and ritonavir with or without ribavirin for 12 weeks of treatment. PegIFN/RBV-experienced subjects received ombitasvir, paritaprevir, and ritonavir in combination with ribavirin for 12 weeks

Treated subjects (N=135) had a median age of 51 years (range: 19 to 70); 63,7% were treatment-naïve, 17.0% were prior pegIFN/RBV null responders, 6.7% were prior pegIFN/RBV partial responders, 12.6% were prior pegIFN/RBV relapsers; 65.2%were male; 8.9% were Black, 14.1% had a body mass index of at least 30 kg/m^2; 69.6% had baseline HCV RNA levels at least 800,000 IU/mL; 78.5% had IL28B non-CC genotype; 6.7% had bridging fibrosis (F3).

Table 16 shows the SVR12 rates for genotype 4 infected subjects, treatment-naïve or previously treated with pegIFN/RBV, who received ombitasvir, paritaprevir and ritonavir with or without ribavirin for 12 weeks in PEARL I.

Table 16. SVR12 for genotype 4-infected, subjects who were treatment-naïve or previously treated with pegIFN/RBV in PEARL I

Treatment outcome	Ombitasvir + paritaprevir + ritonavir* for 12 weeks					
	Treatment-naïve With RBV		Treatment-naïve Without RBV		pegIFN + RBV-experienced With RBV	
	n/N	%	n/N	%	n/N	%
Overall SVR12	42/42	100%	40/44	90.9 %	49/49	100%
Outcome for subjects without SVR12						
On-treatment VF[a]	0/42	0	1/44	2.3%	0/49	0
Relapse[b]	0/42	0	2/44	4.5%	0/49	0
Other[c]	0/42	0	1/44	2.3%	0/49	0

VF = virologic failure

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

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

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

* Ombitasvir tablets, paritaprevir tablets and ritonavir capsules administered separately.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Viekirax 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 Viekirax with dasabuvir have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Table 17 shows mean C_{max} and AUC of Viekirax 25 mg/150 mg/100 mg once daily with dasabuvir 250 mg twice daily following multiple doses with food in healthy volunteers.

Table 17. Geometric mean C_{max}, AUC of multiple doses of Viekirax 150 mg/100 mg/25 mg once daily with dasabuvir 250 mg twice daily with food in healthy volunteers

	C_{max} (ng/ml) (% CV)	AUC (ng*hr/ml) (% CV)
Ombitasvir	127 (31)	1420 (36)
Paritaprevir	1470 (87)	6990 (96)
Ritonavir	1600 (40)	9470 (41)

Absorption

Ombitasvir, paritaprevir and ritonavir were absorbed after oral administration with mean T_{max} of approximately 4 to 5 hours. While ombitasvir exposures increased in a dose proportional manner,

paritaprevir and ritonavir exposures increased in a more than dose proportional manner. Accumulation is minimal for ombitasvir and approximately 1.5- to 2-fold for ritonavir and paritaprevir. Pharmacokinetic steady state for the combination is achieved after approximately 12 days of dosing.

The absolute bioavailability of ombitasvir and paritaprevir was approximately 50% when administered with food as Viekirax.

Effect of paritaprevir/ritonavir on ombitasvir and dasabuvir

In the presence of paritaprevir/ritonavir, dasabuvir exposures decreased by approximately 50% to 60% while ombitasvir exposures increased by 31-47%.

Effect of ombitasvir on paritaprevir/ritonavir and dasabuvir

In the presence of ombitasvir, paritaprevir exposures were minimally affected (5% to 27% change) while dasabuvir exposures increase by approximately 30%.

Effect of dasabuvir on paritaprevir/ritonavir and ombitasvir

In the presence of dasabuvir, paritaprevir exposures increased by 50% to 65% while there was no change in ombitasvir exposures.

Effects of food

Ombitasvir, paritaprevir and ritonavir should be administered with food. All clinical trials with ombitasvir, paritaprevir and ritonavir have been conducted following administration with food.

Food increased the exposure (AUC) of ombitasvir, paritaprevir and ritonavir by up to 82%, 211% and 49%, respectively relative to the fasting state. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal). To maximise absorption, Viekirax should be taken with food without regard to fat or calorie content.

Distribution

Ombitasvir, paritaprevir and ritonavir are highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in subjects with renal or hepatic impairment. The blood to plasma concentration ratios in humans ranged from 0.6 to 0.8 indicating that ombitasvir and paritaprevir were preferentially distributed in the plasma compartment of whole blood. Ombitasvir was approximately 99.9% bound to human plasma proteins. Paritaprevir was approximately 97-98.6% bound to human plasma proteins. Ritonavir was greater than 99% bound to human plasma proteins.

In vitro data indicate that paritaprevir is a substrate for the human hepatic uptake transporters, OATP1B1 and OATP1B3.

Biotransformation

Ombitasvir

Ombitasvir is metabolised via amide hydrolysis followed by oxidative metabolism. Following a 25 mg single dose of ^{14}C-ombitasvir given alone, unchanged parent drug accounted for 8.9% of total radioactivity in human plasma; a total of 13 metabolites were identified in human plasma. These metabolites are not expected to have antiviral activity or off-target pharmacologic activity.

Paritaprevir

Paritaprevir is metabolised predominantly by CYP3A4 and to a lesser extent CYP3A5. Following administration of a single 200 mg/100 mg oral dose of ^{14}C paritaprevir /ritonavir to humans, the parent drug was the major circulating component, accounting for approximately 90% of the plasma radioactivity. At least 5 minor metabolites of paritaprevir have been identified in circulation that accounted for approximately 10% of plasma radioactivity. These metabolites are not expected to have antiviral activity.

Ritonavir

Ritonavir is predominantly metabolised by CYP3A and to a lesser extent, by CYP2D6. Nearly the entire plasma radioactivity after a single 600 mg dose of ^{14}C-ritonavir oral solution in humans was attributed to unchanged ritonavir.

Elimination

Ombitasvir

Following dosing of ombitasvir/paritaprevir/ritonavir with or without dasabuvir, mean plasma half-life of ombitasvir was approximately 21 to 25 hours. Following a single 25 mg dose of ^{14}C- ombitasvir approximately 90% of the radioactivity was recovered in faeces and 2% in urine. Unchanged parent drug accounted for 88% of total radioactivity recovered in faeces, indicating that biliary excretion is a major elimination pathway for ombitasvir.

Paritaprevir

Following dosing of ombitasvir/paritaprevir /ritonavir with or without dasabuvir, mean plasma half-life of paritaprevir was approximately 5.5 hours. Following a 200 mg ^{14}C -paritaprevir dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in faeces with limited radioactivity (8.8%) in urine. Metabolism as well as biliary excretion of parent drug contribute to the elimination of paritaprevir.

Ritonavir

Following dosing of ombitasvir/paritaprevir /ritonavir, mean plasma half-life of ritonavir was approximately 4 hours. Following a 600 mg dose of ^{14}C -ritonavir oral solution, 86.4% of the radioactivity was recovered in the faeces and 11.3% of the dose was excreted in the urine.

In vitro interaction data

Ombitasvir and paritaprevir do not inhibit organic anion transporter (OAT1) *in vivo* and are not expected to inhibit organic cation transporters (OCT1 and OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations. Ritonavir does not inhibit OAT1 and is not expected to inhibit OCT2, OAT3, MATE1 and MATE2K at clinically relevant concentrations.

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 result in approximately 10%

change in ombitasvir exposures, and ≤20% change in paritaprevir 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 55% higher, 100% higher and 15% higher ombitasvir, paritaprevir and ritonavir exposures than male subjects. However, no dose-adjustment based on gender is warranted. A 10 kg change in body weight from 76 kg (median weight in the Phase 3 studies) would results in <10% change in ombitasvir exposures, and no change in paritaprevir exposures. Body weight is not a significant predictor of ritonavir exposures.

Race or ethnicity

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, Asian subjects had 18% to 21% higher ombitasvir exposures, and 37% to 39% higher paritaprevir exposures than non-Asian subjects. The ritonavir exposures were comparable between Asians and non-Asians.

Renal impairment

The changes in ombitasvir, paritaprevir, and ritonavir exposures in subjects with mild, moderate and severe renal impairment are not considered to be clinically significant. No dose adjustment for Viekirax with and without dasabuvir is recommended in HCV-infected patients with mild, moderate or severe renal impairment (see section 4.2). Viekirax has not been studied in HCV-infected patients on dialysis.

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 150 mg, and ritonavir 100 mg, with or without 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.

Following administration of Viekirax and dasabuvir

Compared to the subjects with normal renal function, ombitasvir exposures were comparable in subjects with mild, moderate and severe renal impairment. Compared to the subjects with normal renal function, paritaprevir C_{max} values were comparable, but AUC values were 19%, 33% and 45% higher in mild, moderate and severe renal impairment, respectively. Ritonavir plasma concentrations increased when renal function was reduced: C_{max} and AUC values were 26% to 42% higher**,** 48% to 80% higher and 66% to 114% higher in subjects with mild, moderate and severe renal impairment, respectively.

Following administration of Viekirax

Following administration of Viekirax, the changes in ombitasvir, paritaprevir, and ritonavir exposures in subjects with mild, moderate and severe renal impairment were similar to those observed when Viekirax was administered with dasabuvir, and are not considered to be clinically significant.

Hepatic impairment

The changes in ombitasvir, paritaprevir, and ritonavir exposures in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment are not considered clinically significant. No dose adjustment for Viekirax or dasabuvir is recommended in HCV-infected patients with mild and moderate hepatic impairment (see section 4.2).

Following administration of Viekirax and dasabuvir

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

In subjects with mild hepatic impairment, paritaprevir, ritonavir and ombitasvir mean C_{max} and AUC values decreased by 29% to 48%, 34% to 38% and up to 8%, respectively, compared to subjects with normal hepatic function.

In subjects with moderate hepatic impairment, ombitasvir and ritonavir mean C_{max} and AUC values decreased by 29% to 30% and 30 to 33%, respectively, while paritaprevir mean C_{max} and AUC values increased by 26% to 62% compared to subjects with normal hepatic function. The safety and efficacy of Viekirax have not been established in HCV-infected patients with moderate (Child-Pugh B) hepatic impairment; however, no dose adjustment is expected to be required based on pharmacokinetic studies (see section 4.2).

In subjects with severe hepatic impairment, paritaprevir mean C_{max} and AUC values increased by 3.2-to 9.5-fold; ritonavir mean C_{max} values were 35% lower and AUC values were 13% higher and ombitasvir mean C_{max} and AUC values decreased by 68% and 54%, respectively, compared to subjects with normal hepatic function, therefore, Viekirax must not be used in patients with severe hepatic impairment (see sections 4.2 and 4.4).

Following administration of Viekirax

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg were not evaluated in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. Results from the pharmacokinetic evaluation of the combination of ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg, with dasabuvir 400 mg can be extrapolated to the combination of ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg.

Paediatric population

The pharmacokinetics of Viekirax in paediatric patients has not been established (see section 4.2).

5.3 Preclinical safety data

Ombitasvir

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* mouse micronucleus assays.

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (150 mg/kg/day), resulting in ombitasvir AUC exposures approximately 26-fold higher than those in humans at the recommended clinical dose of 25 mg.

The carcinogenicity study of ombitasvir in rats is ongoing.

Ombitasvir has shown malformations in rabbits at maximal feasible exposures 4-fold higher than the AUC exposure at recommended clinical dose. Malformations at low incidence were observed mainly in the eyes (microphthalmia) and teeth (absent incisors). In mice, an increased incidence of open eye lid was present in foetuses of dams administered ombitasvir; however, the relationship to treatment with ombitasvir is

uncertain. The major, inactive human metabolites of ombitasvir were not teratogenic in mice at exposures approximately 26 times higher than in humans at the recommended clinical dose. Ombitasvir had no effect on fertility when evaluated in mice.
Unchanged ombitasvir was the predominant component observed in the milk of lactating rats, without effect on nursing pups. Ombitasvir-derived material was minimally transferred through the placenta in pregnant rats.

Paritaprevir/ritonavir

Paritaprevir was positive in an *in vitro* human chromosome aberration test. Paritaprevir was negative in a bacterial mutation assay, and in two *in vivo* genetic toxicology assays (rat bone marrow micronucleus and rat liver Comet tests).

Paritaprevir /ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (300 mg/30 mg/kg/day), resulting in paritaprevir AUC exposures approximately 38-fold higher than those in humans at the recommended dose of 150 mg. Similarly, paritaprevir/ritonavir was not carcinogenic in a 2-year rat study up to the highest dosage tested (300 mg/30 mg/kg/day), resulting in paritaprevir AUC exposures approximately 8-fold higher than those in humans at 150 mg.

Paritaprevir/ritonavir has shown malformations (open eye lids) at a low incidence in mice at exposures 32/8-fold higher than the exposure in humans at the recommended clinical dose. Paritaprevir/ritonavir had no effects on embryo-foetal viability or on fertility when evaluated in rats at exposures 2- to 8-fold higher than the exposure in humans at the recommended clinical dose.
Paritaprevir and its hydrolysis product M13 were the predominant components observed in the milk of lactating rats, without effect on nursing pups. Paritaprevir -derived material was minimally transferred through the placenta in pregnant rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Copovidone
Vitamin E polyethylene glycol succinate
Propylene glycol monolaurate
Sorbitan monolaurate
Colloidal anhydrous silica (E551)
Sodium stearyl fumarate

Film-coating
Polyvinyl alcohol (E1203)
Polyethylene glycol 3350
Talc (E553b)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PCTFE aluminium foil blister packs.
56 tablets (multipack carton containing 4 inner cartons of 14 tablets each).

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4XE
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/982/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

Viekirax 12.5 mg / 75 mg / 50 mg film-coated tablets
ombitasvir / paritaprevir / ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film coated tablet contains 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir.

3. LIST OF EXCIPIENTS

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 **two** tablets in the morning

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 Ltd
Maidenhead
SL6 4XE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/982/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

viekirax

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

Viekirax 12.5 mg / 75 mg / 50 mg film-coated tablets
ombitasvir / paritaprevir / ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film coated tablet contains 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir.

3. LIST OF EXCIPIENTS

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 **two** tablets in the morning.

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 Ltd
Maidenhead
SL6 4XE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/982/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

viekirax

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Viekirax 12.5 mg / 75 mg / 50 mg tablets
ombitasvir / paritaprevir / ritonavir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Viekirax 12.5 mg/75 mg/50 mg film-coated tablets
ombitasvir/paritaprevir/ritonavir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 Viekirax is and what it is used for

Viekirax 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). It contains the active substances ombitasvir, paritaprevir and ritonavir.
The combined action of the three active substances stops the hepatitis C virus from multiplying and infecting new cells, thus clearing the virus from your blood over a period of time. Ombitasvir and paritaprevir block two proteins essential for the virus to multiply. Ritonavir acts as a 'booster' to prolong the action of paritaprevir in the body.

Viekirax tablets are taken with other antiviral medicines such as dasabuvir and ribavirin. Your doctor will talk with you about which of these medicines to take with Viekirax.

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

2. What you need to know before you take Viekirax

Do not take Viekirax
- If you are allergic to ombitasvir, paritaprevir, ritonavir, or any of the other ingredients of this medicine (listed in section 6).
- If you have 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 Viekirax is taken with these medicines. These medicines can affect the way Viekirax works and Viekirax can affect the way these other medicines work.

Medicines you must not take with Viekirax	
Medicine or active substance	**Purpose of the medicine**
alfuzosin	for an enlarged prostate
amiodarone	used to correct irregular heartbeats
astemizole, terfenadine	for allergy symptoms. These medicines may be available without a prescription
atorvastatin, lovastatin, simvastatin	to lower blood cholesterol
carbamazepine, phenytoin, phenobarbital	for epilepsy
cisapride	for relieving certain stomach problems
clarithromycin, fusidic acid, rifampicin, telithromycin	for bacterial infections
colchicine in patients who have severe problems with their liver or kidneys	for treating gout attacks
conivaptan	for making the sodium levels in the blood normal
efavirenz, etravirine, lopinavir/ritonavir, saquinavir, tipranavir, nevirapine, indinavir, cobicistat	for HIV infection
enzalutamide	for prostate cancer
ergotamine, dihydroergotamine	for migraine headaches
ergonovine, methylergometrine	used in childbirth
ethinylestradiol-containing medicines such as those contained in most contraceptive pills and vaginal rings used for contraception	for contraception
itraconozole, ketoconozole, posaconazole, voriconazole	for fungal infections
midazolam, triazolam (when taken by mouth)	for anxiety or trouble sleeping
mitotane	for symptoms of malignant tumours of the adrenal glands
pimozide	for schizophrenia
quetiapine	for schizophrenia, bipolar disorder and major depressive disorder
quinidine	for abnormal heart rhythms or malaria
salmeterol	for asthma
sildenafil	when used to treat a heart and lung disorder called “pulmonary arterial hypertension”
St. John’s Wort (*hypericum perforatum*)	a herbal medicine for anxiety and mild depression. This medicine is available without a prescription
ticagrelor	stops blood from clotting

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

Warnings and precautions
Talk to your doctor or pharmacist before taking Viekirax if you have liver disease other than hepatitis C.

When taking Viekirax with dasabuvir, 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

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

Blood tests

Your doctor will test your blood before, during and after your treatment with Viekirax. This is so that your doctor can:

- Decide what other medicines you should take with Viekirax 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 Viekirax or other antiviral medicines your doctor has prescribed for you to use with Viekirax (such as "dasabuvir" and "ribavirin").

Children and adolescents

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

Other medicines and Viekirax

Tell your doctor or pharmacist if you are taking, have recently taken and before starting any other medicines.

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

Tell your doctor or pharmacist before taking Viekirax, 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 Viekirax also if you are using hormonal contraceptives. See the section on contraception below.

Medicines you must tell your doctor about before taking Viekirax	
Medicine or active substance	**Purpose of the medicine**
alprazolam	for anxiety, panic attacks and trouble sleeping
ciclosporin, tacrolimus	to suppress the immune system
colchicine	for treating gout attacks
digoxin, amlodipine, nifedipine, valsartan, diltiazem, verapamil	for heart problems or high blood pressure
furosemide	for the build-up of too much fluid in the body
levothyroxine	for thyroid problems
rilpivirine, darunavir, atazanavir	for HIV infection
omeprazole, lansoprazole, esomeprazole	for stomach ulcers and other stomach problems
imatinib	for the treatment of some cancers of the blood
fluvastatin, pitavastatin, pravastatin, rosuvastatin	to lower blood cholesterol
dabigatran, warfarin	to thin the blood

fexofenadine	for hay fever
s-mephenytoin	for epilepsy
sulfasalazine	for inflammatory bowel disease
repaglinide	for lowering blood sugar
erythromycin	for bacterial infections
steroid or corticosteroid medicines (such as fluticasone)	for many different conditions including serious illnesses and allergies
trazodone	for anxiety and depression

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

Pregnancy
Women must not become pregnant while they or their partner are being treated with Viekirax and ribavirin. This is because ribavirin can cause birth defects or the death of your unborn baby.
- Do not start treatment if you are pregnant.
- Do not become pregnant during treatment.
- If you or your partner becomes pregnant during treatment with Viekirax or in the following 6 months, contact your doctor straight away.

Ask your doctor or pharmacist for advice if you are taking Viekirax with or without ribavirin, and you or your partner are planning to become pregnant.

Read the "Pregnancy" sections of the package leaflets for the other antiviral medicines that you take with Viekirax (such as "dasabuvir" and "ribavirin"). It is important that both men and women read the information.

Contraception

- If you are taking Viekirax with ribavirin, you or your partner must use an effective method of contraception during treatment and for 6 months after treatment is finished. Ask your doctor about the best contraception for you.
- Talk to your doctor before taking Viekirax if you are using a contraceptive medicine that contains ethinylestradiol. Your doctor will ask you to stop and change to a different type of contraceptive medicine during your treatment with Viekirax.

Read the "Contraception" section of the package leaflets for the other antiviral medicines that you take with Viekirax (such as "dasabuvir" and "ribavirin"). It is important that both men and women read the information.

Breastfeeding
You should not breast-feed during treatment with Viekirax. It is not known whether the active substances in Viekirax (ombitasvir, paritaprevir and ritonavir) pass into breast milk.

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

3. How to take Viekirax

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

Viekirax tablets are usually taken with other anti-viral medicines such as “dasabuvir” and “ribavirin”.

How much to take
The recommended dose is two tablets taken together in the morning.

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

How long to take Viekirax for
You will take Viekirax for either 12 or 24 weeks. Your doctor will tell you how long your treatment will last. Do not stop taking Viekirax 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 Viekirax 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 that you can easily describe what you have taken.

If you forget to take Viekirax
It is important not to miss a dose of this medicine. If you do miss a dose and it is:
- **More than 12 hours** until your next dose - take the missed dose with food as soon as possible.
- **Less than 12 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.

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

Side effects when taking Viekirax with dasabuvir:
Common: may affect up to 1 in 10 people
- Itching

Side effects when taking Viekirax with dasabuvir and 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).

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

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 Viekirax

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 Viekirax contains
- Each tablet contains 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir.
- The other ingredients are:
  - Tablet core: copovidone, vitamin E, polyethylene glycol succinate, propylene glycol monolaurate, sorbitan monolaurate, colloidal anhydrous silica (E551), sodium stearyl fumarate.
  - Tablet film-coating: polyvinyl alcohol (E1203), polyethylene glycol 3350, talc (E553b), titanium dioxide (E171) and red iron oxide (E172).

What Viekirax looks like and contents of the pack
Viekirax tablets are pink, oblong film-coated tablets of dimmensions 18.8 mm x 10.0 mm, marked with 'AV1'. Viekirax tablets are packed into foil blisters containing 2 tablets. Each carton contains 56 tablets (multipack carton containing 4 inner cartons of 14 tablets each).

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SL6 4XE
United Kingdom

Manufacturer
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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.