

PRODUCT INFORMATION

TECHNIVIE COMBINATION THERAPY PACK

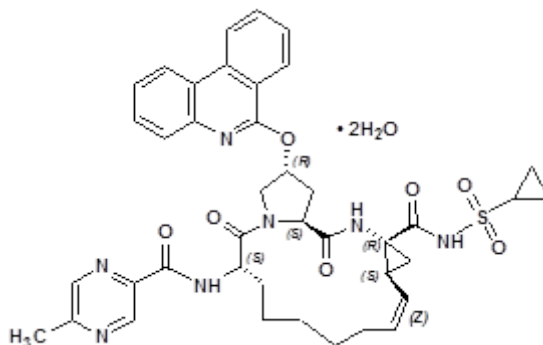
NAME OF THE MEDICINE

TECHNIVIE is a fixed dose combination tablet containing paritaprevir/ritonavir/ombitasvir
75/50/12.5 mg tablets.

Chemical Structure and Description of each Active Pharmaceutical Ingredient

Paritaprevir

Paritaprevir drug substance is manufactured as a dihydrate; however, it is dehydrated during the drug product manufacturing process and is amorphous and anhydrous in the final product. Paritaprevir dihydrate is chemically designated (2*R*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-*N*-(cyclopropylsulfonyl)-6-[[[5-methylpyrazin-2-yl)carbonyl]amino]-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13*a*,14,15,16,16atetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14*a*(5*H*)-carboxamide dihydrate. The molecular formula is $C_{40}H_{43}N_7O_7S \cdot 2H_2O$ (dihydrate) and the molecular weight for the drug substance is 801.91 (dihydrate). Paritaprevir dihydrate has the following structural formula:

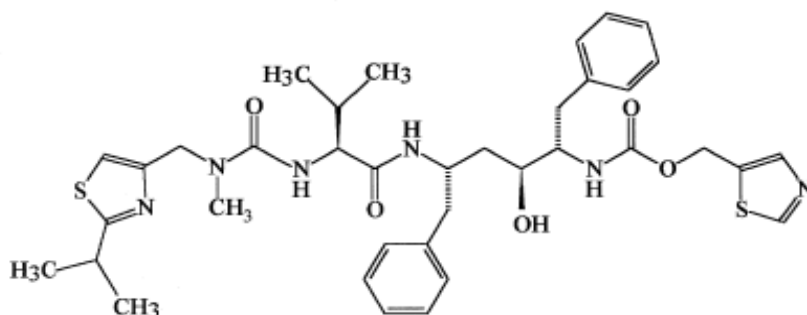


CAS Number: 1456607-71-8

Paritaprevir dihydrate is a white to off-white powder with very low water solubility. Paritaprevir dihydrate has a pKa of 4.6 at 25°C.

Ritonavir

Ritonavir is chemically designated as [5*S*-(5*R**,8*R**,10*R**,11*R**)]10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester. The molecular formula is $C_{37}H_{48}N_6O_5S_2$ and the molecular weight is 720.95. Ritonavir has the following structural formula:

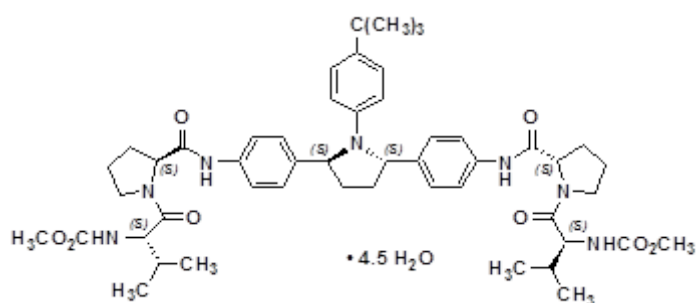


CAS Number: 155214-67-5

Ritonavir is a white to light tan powder practically insoluble in water and freely soluble in methanol and ethanol. Ritonavir has a pKa of 2.8.

Ombitasvir

Ombitasvir drug substance is manufactured as a hydrate; however, it is dehydrated during the drug product manufacturing process and is amorphous and anhydrous in the final product. Ombitasvir hydrate is chemically designated as dimethyl (((2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl)bis{benzene-4,1-diylcarbonyl(2*S*)pyrrolidine-2,1-diyl}[(2*S*)-3-methyl-1-oxobutane-1,2-diyl])biscarbamate hydrate. The molecular formula is C₅₀H₆₇N₇O₈ • 4.5H₂O (hydrate) and the molecular weight for the drug substance is 975.20 (hydrate). Ombitasvir hydrate has the following structural formula:



CAS Number: 1456607-70-7

Ombitasvir hydrate is a white to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. Ombitasvir hydrate has a pKa of 2.5 at 25°C.

DESCRIPTION

TECHNIVIE is a fixed-dose combination tablet containing paritaprevir, ritonavir and ombitasvir for oral administration.

Paritaprevir, ritonavir and ombitasvir fixed dose combination tablet includes a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), a hepatitis C virus NS5A inhibitor (ombitasvir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby providing increased plasma concentration of paritaprevir.

Paritaprevir, ritonavir, and ombitasvir are co-formulated as film-coated immediate release tablets. The tablets also contain copovidone, tocofersolan, propylene glycol monolaurate, sorbitan monolaurate, silicon dioxide, sodium stearyl fumarate and Opadry II pink 85F140088 (polyvinyl alcohol, titanium dioxide, macrogol, purified talc, and iron oxide red). The tablets do not contain gluten. The strength for the fixed dose combination tablet is 75 mg paritaprevir/50 mg ritonavir/12.5 mg ombitasvir.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: J05AX67

Mechanism of Action

TECHNIVIE combines two direct-acting hepatitis C virus antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Paritaprevir

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

Ritonavir

Ritonavir is not active against HCV. Ritonavir is a pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (i.e. area under the curve).

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A, which is necessary for viral replication and virion assembly.

Activity in Cell Culture and/or Biochemical Studies

Paritaprevir

In a biochemical assay, paritaprevir inhibited the proteolytic activity of a recombinant HCV genotype 4a NS3/4A protease enzyme with an IC_{50} value of 0.16 nM. The EC_{50} values of paritaprevir against HCV replicons containing NS3 from a single isolate each of genotype 4a and genotype 4d were 0.09 nM and 0.015 nM, respectively. Paritaprevir inhibited the activity of NS3/4A enzymes from single isolates of genotypes 1a, 1b, 2a, 2b, and 3a with IC_{50} values of 0.18 nM, 0.43 nM, 2.4 nM, 6.3 nM, and 14.5 nM, respectively. Paritaprevir had EC_{50} values of 1.0 nM, 0.21 nM, 5.3 nM, 19 nM, and 0.68 nM against replicon cell lines representing genotypes 1a-H77, 1b-Con1, 2a-JFH1, 3a and 6a, respectively.

Ritonavir

Ritonavir did not exhibit a direct antiviral effect on the replication of HCV subgenomic replicons, and the presence of ritonavir did not affect the *in vitro* antiviral activity of paritaprevir.

Ombitasvir

In replicon cell culture assays, the EC_{50} values of ombitasvir against HCV replicons containing NS5A from a single isolate each of genotype 4a and genotype 4d were 1.7 pM and 0.38 pM, respectively. Ombitasvir had a median EC_{50} value of 0.21 pM (range 0.10 pM to 0.36 pM; n=9) against transient HCV replicons containing NS5A genes from a panel of genotype 4a isolates from treatment-naïve subjects. Ombitasvir had EC_{50} values of 14 pM, 5.0 pM, 12 pM, 4.3 pM, 19 pM, 3.2 pM, and 366 pM against replicon cell lines representing genotypes 1a-H77, 1b-Con1, 2a, 2b, 3a, 5a and 6a, respectively.

Resistance

In Cell Culture

Exposure of HCV genotype 4a replicons to ombitasvir or paritaprevir resulted in the emergence of drug resistant replicons carrying amino acid substitutions in NS5A or NS3, respectively. Amino acid substitutions in NS5A or NS3 selected in cell culture or identified in clinical study PEARL-I were phenotypically characterised in genotype 4 replicons.

For ombitasvir, in an HCV genotype 4a replicon, NS5A substitution L28V reduced ombitasvir antiviral activity by 21-fold. In an HCV genotype 4d replicon, substitutions L28V alone and L28V in combination with T58S reduced ombitasvir antiviral activity by 310- and 760-fold, respectively.

Ombitasvir activity against an HCV genotype 4d replicon was not reduced by a T58P polymorphism, which represents the consensus sequence observed at this position for HCV genotype 4a and 4d subjects in PEARL-I.

For paritaprevir, in an HCV genotype 4a replicon, NS3 substitutions R155C, A156T/V, and D168H/V reduced paritaprevir antiviral activity by 40- to 323-fold. In an HCV genotype 4d replicon, NS3 substitutions Y56H and D168V reduced paritaprevir antiviral activity by 8- and 313-fold, respectively, while a combination of Y56H and D168V reduced the activity of paritaprevir by 12,533-fold.

In Clinical Studies

In the clinical study PEARL-I, three subjects with HCV genotype 4 infection experienced virologic failure (2 post-treatment relapse, 1 on-treatment failure). All 3 virologic failures were observed in a regimen containing paritaprevir/ritonavir and ombitasvir without ribavirin (RBV). Treatment-emergent, resistance-associated substitutions were detected at the time of failure in all 3 subjects and included D168V (with or without Y56H) in NS3, and L28S and L28V (with or without M31I or T58S) in NS5A.

In the clinical study AGATE-I, one subject with HCV genotype 4a infection experienced virologic failure (on-treatment failure). Treatment-emergent resistance-associated substitutions were not detected in NS3 at the time of failure, and L28M and Y93H were detected in NS5A.

Persistence of Resistance-Associated Substitutions

In HCV genotype 1, persistence of ombitasvir and paritaprevir resistance-associated substitutions through 24 or 48 weeks post-treatment has been observed in subjects who experienced virologic failure with ombitasvir- and paritaprevir-containing regimens. The long-term clinical impact of the emergence or persistence of virus containing ombitasvir or paritaprevir resistance-associated substitutions is unknown.

The persistence of ombitasvir and paritaprevir resistance-associated amino acid substitutions in NS5A and NS3, respectively, was assessed in HCV genotype 4-infected subjects in clinical study PEARL-I. Treatment-emergent variants L28S/V and M31I in NS5A remained detectable at post-treatment Week 48 in 2 of 3 subjects. NS3 variant D168V was not detected at post-treatment week 48.

Effect of Baseline HCV Polymorphisms on Treatment Response

Phylogenetic analysis of HCV sequences from genotype 4-infected subjects in the clinical study PEARL-I, identified 7 HCV genotype 4 subtypes (4a, 4b, 4c, 4d, 4f, 4g/4k, 4o). Most subjects were infected with either subtype 4a (38%) or 4d (52%); 1 to 7 subjects were infected with each of the other genotype 4 subtypes. Three subjects who experienced virologic failure with the regimen containing paritaprevir/ritonavir and ombitasvir without ribavirin were infected with HCV subtype 4d.

Phylogenetic analysis of HCV sequences from genotype 4-infected subjects in the clinical study AGATE-I, identified 14 HCV genotype 4 subtypes (4a, 4c, 4d, 4e, 4f, 4h, 4k, 4l, 4n, 4o, 4p, 4q, 4r, 4t). Most subjects were infected with either subtype 4a (54%) or 4d (26%); 1 to 4 subjects were infected with each of the other genotype 4 subtypes. The single subject who experienced virologic failure in the clinical study AGATE-I was infected with HCV subtype 4a.

Baseline HCV polymorphisms are not expected to impact the likelihood of achieving SVR when TECHNIVIE is used as recommended to treat HCV genotype 4 infected patients, based on the low virologic failure rate observed in PEARL-I and AGATE-I.

Cross-resistance

Cross-resistance may occur among NS5A inhibitors and among NS3/4A protease inhibitors within each individual class. The impact of prior ombitasvir or paritaprevir treatment experience on the efficacy of other NS5A inhibitors or NS3/4A protease inhibitors has not been studied. Similarly, the efficacy of TECHNIVIE has not been studied in subjects who have failed prior treatment with another NS5A inhibitor, NS3/4A protease inhibitor, or NS5B inhibitor.

Pharmacodynamic interactions

Co-administration with enzyme inducers may increase the risk of adverse events and ALT elevations. Co-administration with ethinylestradiol may increase the risk of ALT elevations (see INTERACTIONS WITH OTHER MEDICINES).

Pharmacokinetics

The pharmacokinetic properties of the combination of paritaprevir, ritonavir and ombitasvir have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Table 1 shows mean C_{max} and AUC_{0-24} of paritaprevir/ritonavir/ombitasvir 150/100/25 mg once daily following multiple doses with food in healthy volunteers.

Table 1: Geometric Mean C_{max} and AUC_{0-24} of Multiple Doses of Paritaprevir/Ritonavir/Ombitasvir 150/100/25 mg Once Daily with Food in Healthy Volunteers

	C_{max} (ng/mL)	AUC_{0-24} (ng*hr/mL)
paritaprevir	194	2276
ombitasvir	82	1239
ritonavir	543	6072

Absorption

Paritaprevir/ritonavir/ombitasvir was 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 when administered with ritonavir as TECHNIVIE was approximately 48.1% and 52.6%, respectively.

Effects of Food on Oral Absorption

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

Food increased the exposure (AUC) of paritaprevir, ombitasvir and ritonavir by up to 211%, 82% 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, TECHNIVIE should be taken with food without regard to fat or calorie content.

Distribution

Paritaprevir

Paritaprevir was approximately 97 to 98.6% bound to human plasma proteins over a concentration range of 0.08 to 8 µg per mL. The mean blood-to-plasma concentration ratio was 0.7. The volume of distribution (V) was 103 L.

Ombitasvir

Ombitasvir was approximately 99.9% bound to human plasma proteins over a concentration range of 0.09 to 9 µg per mL. The mean blood-to-plasma concentration ratio was 0.49. The volume of distribution (V) was 173 L.

Ritonavir

Ritonavir was greater than 99% bound to human plasma proteins over a concentration range of 0.007 to 22 µg per mL. The mean blood-to-plasma concentration ratio was 0.6.

Metabolism

Paritaprevir

Paritaprevir is metabolised predominantly by CYP3A4 and to a lesser extent CYP3A5. Following administration of a single 200/100 mg oral dose of ¹⁴C 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.

Ombitasvir

Ombitasvir is metabolised via amide hydrolysis followed by oxidative metabolism. Following a 25 mg single dose of ¹⁴C-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 pharmacological 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 ¹⁴C-ritonavir oral solution in humans was attributed to unchanged ritonavir.

Elimination

Paritaprevir

Following dosing of paritaprevir/ritonavir/ombitasvir, mean plasma half-life of paritaprevir was approximately 5.5 hours. Following a 200 mg ¹⁴C-paritaprevir dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in faeces with limited radioactivity (8.8%) in urine.

Ombitasvir

Following dosing of paritaprevir/ritonavir/ombitasvir, mean plasma half-life of ombitasvir was approximately 21-25 hours. Following a 25 mg ¹⁴C-ombitasvir dose, approximately 90.2% of the radioactivity was recovered in faeces with limited radioactivity (1.91%) in urine.

Ritonavir

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

Implications for Drug Interactions

Potential for TECHNIVIE 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 metabolising enzymes that are affected by TECHNIVIE. See INTERACTIONS WITH OTHER MEDICINES 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 TECHNIVIE with medicinal products primarily metabolised 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 CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES).

CYP3A substrates evaluated in drug interaction studies which may require dose adjustment and/or clinical monitoring include (see Table 5) 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 metabolised by CYP3A, drug interaction studies indicate that no dose adjustment is needed when co-administering these medicinal products with TECHNIVIE (see Table 5).

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 TECHNIVIE 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 5), fexofenadine, repaglinide and angiotensin II receptor antagonists (e.g., valsartan).

OATP1B1/3 substrates evaluated in drug interaction studies include pravastatin and rosuvastatin (see Table 5).

Medicinal products transported by BCRP

Paritaprevir and ritonavir are inhibitors of BCRP *in vivo*. Co-administration of TECHNIVIE 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 5).

BCRP substrates evaluated in drug interaction studies include rosuvastatin (see Table 5).

Medicinal products transported by P-gp in the intestine

Co-administration of digoxin with TECHNIVIE may result in increased digoxin plasma concentrations (see Table 5). TECHNIVIE 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 and ombitasvir are inhibitors of UGT1A1. Co-administration of TECHNIVIE with medicinal products that are primarily metabolised 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 INTERACTIONS WITH OTHER MEDICINES for specific advice on raltegravir and buprenorphine, which have been evaluated in drug interaction studies.

Medicinal products metabolised by CYP2C19

Co-administration of TECHNIVIE can decrease exposures of medicinal products that are metabolised 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 5).

Medicinal products metabolised by CYP2C9

TECHNIVIE 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

TECHNIVIE 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, TECHNIVIE is not expected to affect medicinal products which are primarily excreted by the renal route via these transporters.

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

Medicinal products that inhibit CYP3A4

Co-administration of TECHNIVIE with strong inhibitors of CYP3A may increase paritaprevir concentrations (see Table 5).

Enzyme inducers

Co-administration of TECHNIVIE with medicinal products that are moderate or strong enzyme inducers is expected to decrease paritaprevir, ritonavir and ombitasvir plasma concentrations and reduce their therapeutic effect. Contraindicated enzyme inducers are provided under CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES.

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 TECHNIVIE 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.

Special Populations

Renal Impairment

Paritaprevir/ritonavir/ombitasvir

The single dose pharmacokinetics of paritaprevir, ritonavir and ombitasvir were evaluated in non-HCV infected subjects with mild (CLcr: 60 to 89 mL/min), moderate (CLcr: 30 to 59 mL/min), and severe (CLcr: 15 to 29 mL/min) renal impairment.

Overall, changes in exposure of paritaprevir, ritonavir and ombitasvir in non-HCV infected subjects with mild-, moderate- and severe renal impairment are not expected to be clinically relevant.

Relative to subjects with normal renal function, paritaprevir and ritonavir AUC values increased by 11% and 40%, respectively, while ombitasvir AUC values were unchanged in subjects with mild renal impairment.

Relative to subjects with normal renal function, paritaprevir and ritonavir AUC values increased by 19% and 76%, respectively, while ombitasvir AUC values were unchanged in subjects with moderate renal impairment.

Relative to subjects with normal renal function, paritaprevir and ritonavir AUC values increased by 25% and 108%, respectively, while ombitasvir AUC values were unchanged in subjects with severe renal impairment.

No dose adjustment for TECHNIVIE is recommended in HCV-infected subjects with mild, moderate or severe renal impairment.

Hepatic Impairment

Pharmacokinetics of the combination of paritaprevir 200 mg, ombitasvir 25 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 paritaprevir 200 mg, ombitasvir 25 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.

The changes in paritaprevir, ombitasvir and ritonavir exposures in subjects with mild and moderate hepatic impairment are not considered clinically significant. No dosage adjustment of TECHNIVIE is required in patients with mild hepatic impairment (Child-Pugh A). TECHNIVIE is not recommended in patients with moderate hepatic impairment (Child-Pugh B). A decision to initiate treatment in patients with Child-Pugh B should be guided by assessment of the potential benefits and risks for the individual. TECHNIVIE is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS and PRECAUTIONS).

Elderly

No dose adjustment is necessary for paritaprevir/ritonavir/ombitasvir in elderly patients.

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies of genotype 1-infected subjects, 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 $\leq 20\%$ change in paritaprevir exposures. There is no pharmacokinetic information in patients >75 years.

Paediatric Population (<18 years)

The pharmacokinetics, safety and efficacy of TECHNIVIE in paediatric patients have not been established.

Race or Ethnicity

No dose adjustment is necessary for TECHNIVIE based on race or ethnicity. Based on population pharmacokinetic analysis of data from Phase 3 clinical studies of genotype 1-infected subjects, Asian subjects had 18% to 21%, 37% to 39% and 29% to 39% higher ombitasvir and paritaprevir exposures respectively, than non-Asian subjects. The ritonavir exposures were comparable between Asians and non-Asians. However, patient numbers in the clinical trials were not sufficient to definitively address possible differences in pharmacokinetics and toxicity profiles in specific ethnic groups such as Asian patients.

Sex or Body weight

No dose adjustment is necessary for TECHNIVIE based on gender or body weight.

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies of genotype 1-infected subjects, female subjects would have approximately 55%, 100% and 15% higher ombitasvir, paritaprevir and ritonavir exposures (AUC), respectively, than male subjects. A 10 kg change in body weight from 76 kg (median weight in the Phase 3 studies) would result in $<10\%$ change in ombitasvir exposures, and no change in paritaprevir exposures. Body weight is not a significant predictor of ritonavir exposures.

CLINICAL TRIALS

The efficacy and safety of paritaprevir, ritonavir and ombitasvir with or without ribavirin was evaluated in three clinical trials in subjects with genotype 4 (GT4) chronic hepatitis virus (HCV) infection. In each trial, paritaprevir, ritonavir and ombitasvir 150/100/25 mg once daily was administered with food and weight based ribavirin for 12 weeks. The ribavirin dosage 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. The primary endpoint in each trial was sustained virologic response defined as HCV RNA below the lower limit of quantification ($<LLOQ$) 12 weeks after the end of treatment (SVR12) using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System, which has an LLOQ of 25 IU per mL (except for AGATE-II, in which the Roche AmpliPrep/COBAS TaqMan

HCV Test version 2.0 with an LLOQ of 15 IU/mL was used at a designated laboratory in Egypt). Previous exposure to HCV direct-acting antivirals was prohibited.

PEARL-I – Genotype 4, Treatment-Naïve or Treatment-Experienced Subjects without Cirrhosis

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 either treatment-naïve or did not achieve SVR with prior treatment with pegylated interferon/ribavirin (pegIFN/RBV). Treatment-naïve subjects were randomised in a 1:1 ratio to receive paritaprevir, ritonavir and ombitasvir 150/100/25 mg with food with or without ribavirin for 12 weeks. PegIFN/RBV treatment-experienced subjects received paritaprevir, ritonavir and ombitasvir 150/100/25 mg once-daily with food in combination with ribavirin for 12 weeks.

Treated subjects (N=135) had a median age of 51 years (range: 19 to 70); 64% were treatment-naïve, 17% were prior pegIFN/RBV null responders; 7% were prior pegIFN/RBV partial responders, 13% were prior pegIFN/RBV relapsers; 65% were male; 9% were Black; 14% had a body mass index at least 30 kg/m²; 70% had baseline HCV RNA levels at least 800,000 IU/mL; 79% had IL28B (rs12979860) non-CC genotype; 7% had bridging fibrosis (F3).

Table 2 presents the SVR rates.

Table 2. SVR for HCV Genotype 4-Infected Subjects without Cirrhosis

Treatment outcome	Paritaprevir + Ritonavir + Ombitasvir* with RBV for 12 weeks		Paritaprevir + Ritonavir + Ombitasvir* for 12 weeks
	Treatment-naïve	Treatment-experienced	Treatment-naïve
	% (n/N)	% (n/N)	% (n/N)
Overall SVR12	100 % (42/42)	100% (49/49)	91% (40/44)
Outcome for subjects without SVR12			
On-treatment VF ^a	0% (0/42)	0% (0/49)	2% (1/44)
Relapse ^b	0% (0/42)	0% (0/49)	5% (2/42)
Other ^c	0% (0/42)	0% (0/49)	2% (1/44)
Overall SVR24	100 % (42/42)	100% (49/49)	86% (38/44) ^d
VF = virologic failure			
* Administered as separate paritaprevir tablets, ritonavir capsules and ombitasvir tablets.			
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.			

lost to follow-up).

d. Two subjects who achieved SVR12 failed to achieve SVR24 due to reasons other than on-treatment VF or relapse.

AGATE-I – Genotype 4, Treatment-Naïve or Treatment-Experienced Subjects with Compensated Cirrhosis

AGATE-I was a randomised, global multicentre, open-label trial conducted in subjects with genotype 4 chronic hepatitis C virus infection with compensated cirrhosis who were treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV.

Subjects had a median age of 56 years (range: 43 to 81); 51% were treatment-naïve, 29% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 12% were prior pegIFN/RBV relapsers; 76% were male; 17% were Black; 29% had a body mass index of at least 30 kg/m²; 76% had baseline HCV RNA levels of at least 800,000 IU per mL; 86% had IL28B (rs12979860) non-CC genotype; 12% had platelet counts of less than 90 x 10⁹ per L; and 5% had albumin less than 3.5 mg per dL.

Table 3 presents the SVR12 rates.

Table 3. SVR12 for HCV Genotype 4-Infected Subjects with Compensated Cirrhosis

Endpoint	Paritaprevir + Ritonavir + Ombitasvir* with RBV for 12 Weeks
	% (n/N)
SVR12, % (n/N)	97% (57/59)
Outcome for subjects without SVR12	
On-treatment virologic failure ^a	2% (1/59)
Post-treatment relapse ^b	0% (0/57)
Other ^c	2% (1/59)

VF = virologic failure

*Administered as co-formulated tablets

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 log₁₀ 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. lost to follow-up).

AGATE-II – Genotype 4, Treatment-Naïve or Treatment-Experienced Subjects without Cirrhosis or with Compensated Cirrhosis

AGATE-II was an open-label, multicentre, randomised trial conducted in subjects in Egypt with genotype 4 chronic hepatitis C infection without cirrhosis or with compensated cirrhosis, who were treatment-naïve or treatment experienced with pegIFN/RBV. Subjects without cirrhosis received 12 weeks of co-formulated paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin and subjects

with compensated cirrhosis received 12 or 24 weeks of co-formulated paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin.

Subjects without cirrhosis had a median age of 51 years (range: 21 to 71); 49% were treatment-naïve, 33% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 10% were prior pegIFN/RBV relapsers; 70% were male; 2% were Black; 36% had a body mass index of at least 30 kg/m². The SVR12 rate for subjects without cirrhosis treated for 12 weeks was 94.0% (94/100); 1 subject experienced on-treatment virologic failure, 3 experienced relapse and 2 did not achieve SVR12 due to reasons other than on-treatment virologic failure or relapse.

Subjects with compensated cirrhosis treated for 12 weeks of therapy had a median age of 58 years (range: 41 to 68); 48% were treatment-naïve, 29% were prior pegIFN/RBV null responders; 6% were prior pegIFN/RBV partial responders, 16% were prior pegIFN/RBV relapsers; 94% were male; 6% were Black; 42% had a body mass index of at least 30 kg/m²; and 6% had albumin less than 3.5 mg per dL. The SVR12 rate for subjects with compensated cirrhosis treated for 12 weeks was 96.8% (30/31); 1 subject did not achieve SVR12 due to reasons other than on-treatment virologic failure or relapse.

INDICATIONS

TECHNIVIE is indicated in combination with ribavirin for the treatment of adult patients with genotype 4 chronic hepatitis C virus (HCV) infection.

CONTRAINDICATIONS

- The contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- TECHNIVIE is contraindicated:
 - In patients with severe hepatic impairment (Child-Pugh C) due to risk of potential toxicity [see *Use in Specific Populations and Clinical Pharmacology*].
 - With drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
 - With drugs that are moderate or strong inducers of CYP3A and may lead to reduced efficacy of TECHNIVIE.
 - In patients with known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome).

Table 4 lists drugs that are contraindicated with TECHNIVIE (see INTERACTIONS WITH OTHER MEDICINES).

Table 4– Drugs that are contraindicated with TECHNIVIE

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCl	Potential for hypotension.
Antianginal	Ranolazine	Potential for serious and/or life-threatening reactions
Antiarrhythmics	Amiodarone, quinidine	Potential for cardiac arrhythmias.

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
	Dronedarone	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
Antihistamines (for systemic use)	Astemizole, terfenadine	Potential for cardiac arrhythmias.
Antigout medications	Colchicine (in patients with renal or hepatic impairment)	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antimycobacterial	Rifampicin	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
Antipsychotic	Blonanserin	No information on potential effects is currently available
	Lurasidone	Potential for serious and/or life-threatening reactions
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine	Acute ergot toxicity characterised by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinylestradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives	Potential for ALT elevations [see Precautions].
GI motility agent	Cisapride	Potential for cardiac arrhythmias.
Herbal product	St. John's Wort (<i>Hypericum perforatum</i>)	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
HMG-CoA reductase inhibitors	Lovastatin, simvastatin, atorvastatin	Potential for myopathy including rhabdomyolysis.
Long acting Beta-Adrenoceptor agonist	Salmeterol	The combination may result in increased risk of cardiovascular adverse events associated with

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
		salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Neuroleptics	Pimozide	Potential for cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor	Efavirenz	Co-administration of efavirenz based regimens with paritaprevir and ritonavir was poorly tolerated and resulted in liver enzyme elevations.
Phosphodiesterase-5 (PDE5) inhibitor	Sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)	There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Platelet aggregation inhibitors excluding heparin	Ticagrelor	Increased potential for ticagrelor associated adverse events.
Sedatives/hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Co-administration of triazolam or orally administered midazolam with TECHNIVIE may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.
Steroid antibacterials	Fusidic acid	Increased potential for fusidic acid associated adverse events.
Anticancer agents	Mitotane, enzalutamide	Increased potential for mitotane and enzalutamide associated adverse events.

PRECAUTIONS

TECHNIVIE efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes TECHNIVIE or other direct-acting antiviral agents.

Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis

Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported from postmarketing sources in patients treated with paritaprevir/ritonavir/ombitasvir with and without dasabuvir and with and without ribavirin. Most patients with these severe outcomes had evidence of advanced or decompensated cirrhosis prior to initiating therapy. Reported cases typically occurred within one to four weeks of initiating therapy and were

characterised by the acute onset of rising direct serum bilirubin levels without ALT elevations in association with clinical signs and symptoms of hepatic decompensation. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Paritaprevir/ritonavir/ombitasvir with or without dasabuvir is not recommended in patients with moderate hepatic impairment (Child-Pugh B). A decision to initiate treatment in patients with Child-Pugh B should be guided by assessment of the potential benefits and risks for the individual. Paritaprevir/ ritonavir/ombitasvir with or without dasabuvir is contraindicated in patients with severe hepatic impairment (Child-Pugh C).

For patients with cirrhosis:

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

ALT Elevations

During clinical trials with paritaprevir, ritonavir and ombitasvir with dasabuvir and with or without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects. These ALT elevations were significantly more frequent in female subjects who were using ethinylloestradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings (see CONTRAINDICATIONS). ALT elevations typically occurred during the first 4 weeks of treatment and declined within approximately two weeks of onset with continued dosing of paritaprevir, ritonavir and ombitasvir with dasabuvir and with or without ribavirin.

Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with TECHNIVIE (see CONTRAINDICATIONS). Alternative contraceptive agents or methods of contraception (e.g., progestin only contraception or non-hormonal methods) are recommended during TECHNIVIE therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with TECHNIVIE.

Subjects using oestrogens other than ethinyl estradiol, such as oestradiol and conjugated oestrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any oestrogens (1%). No additional monitoring of ALT is required outside of local recommendations and routine clinical practice guidelines.

If ALT is found to be elevated above baseline levels, it should be monitored closely.

- Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discoloured urine or faeces (see Serum Bilirubin Elevations under PRECAUTIONS).
- Discontinue TECHNIVIE if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

Risks Associated with Ribavirin Combination Treatment

The warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to the combination regimen with TECHNIVIE. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.

Co-administration with Drugs Metabolised by CYP3A

Also refer to CONTRAINDICATIONS, INTERACTIONS WITH OTHER MEDICINES, Table 5 and PHARMACOKINETICS-Implications for Drug Interactions.

Use with Fluticasone (glucocorticoids metabolised by CYP3A)

Use caution when administering TECHNIVIE 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 TECHNIVIE and glucocorticoids, particularly long-term use, should only be initiated if the potential benefit of treatment outweighs the risk of systemic corticosteroid effects.

Use with Quetiapine

The use of TECHNIVIE with quetiapine is not recommended due to increases in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose to 1/6th of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for the recommendations on adverse reaction monitoring.

Use with Colchicine

The interaction between TECHNIVIE 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 TECHNIVIE is required. In patients with renal or hepatic impairment, use of colchicine with TECHNIVIE is contraindicated (see CONTRAINDICATIONS).

Use with Statins

Atorvastatin, simvastatin and lovastatin are contraindicated (see CONTRAINDICATIONS).

Pitavastatin and fluvastatin

The interactions between pitavastatin and fluvastatin and TECHNIVIE have not been investigated. Theoretically, TECHNIVIE is expected to increase the exposure to pitavastatin and fluvastatin. A temporary suspension of pitavastatin and fluvastatin is recommended for the duration of treatment with TECHNIVIE. If statin treatment is required during the treatment period, a switch to a reduced dose of pravastatin or rosuvastatin is possible (see Table 5).

Hepatic Impairment

No dose adjustment of TECHNIVIE is required in patients with mild hepatic impairment (Child-Pugh A). TECHNIVIE is not recommended in patients with moderate hepatic impairment (Child-Pugh B). A decision to initiate treatment in patients with Child-Pugh B should be guided by assessment of the potential benefits and risks for the individual. TECHNIVIE is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS and Pharmacokinetics).

HCV/HIV-1 co-infected Subjects

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

Drug interactions need to be carefully taken into account in the setting of HIV co-infection. For extensive details on Drug Interactions with antiretroviral therapy, refer to INTERACTIONS WITH OTHER MEDICINES.

Effects on Fertility

Paritaprevir/ritonavir

Paritaprevir/ritonavir had no effects on embryofoetal viability or on fertility when evaluated in rats up to the highest dose of 300/30 mg/kg/day. Paritaprevir and ritonavir AUC exposures at this dosage were approximately 5 and 3-fold the exposure in humans at the recommended clinical dose.

Ombitasvir

Ombitasvir had no effects on embryofoetal viability or on fertility when evaluated in mice up to the highest dose of 200 mg/kg/day. Ombitasvir AUC exposures at this dosage were approximately 23-fold (female) or 29-fold (male) the exposure in humans at the recommended clinical dose.

Use in Pregnancy

Ribavirin Pregnancy Category X

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients when TECHNIVIE is used with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, ribavirin is contraindicated in women who are pregnant and in men whose female partners are pregnant. Women of childbearing potential and their male partners should not receive ribavirin unless they are using two reliable forms of contraception during treatment with ribavirin and for 6 months after treatment (see **PRECAUTIONS**, and ribavirin prescribing information).

TECHNIVIE Pregnancy Category B3

Since there are no adequate and well-controlled studies with TECHNIVIE in pregnant women, it should be used during pregnancy only if the benefits outweigh the risks.

No effects on embryofoetal development have been noted in studies in animals with paritaprevir/ritonavir (in combination), ombitasvir and its major inactive human metabolites (M29, M36). For paritaprevir/ritonavir, the highest doses tested produced exposures equal to 143-fold (mouse) or 12-fold (rat) for paritaprevir (and 6-fold (mouse) or 3-fold (rat) for ritonavir) the exposures in humans at the recommended clinical doses. For ombitasvir, the highest dose tested produced exposures equal to 29-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26 times higher in mice than in humans at the recommended clinical dose.

Developmental toxicity has been observed in embryofetal development studies with ritonavir alone. In rats, early resorptions, decreased foetal body weight and ossification delays and developmental variations occurred at a maternally toxic dosage of 75 mg/kg/day (5-fold the exposure in humans at the recommended clinical dose). A slight increase in the incidence of cryptorchidism was also noted in rats given 35 mg/kg/day (4-fold the exposure in humans at the recommended clinical dose). Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased fetal weights) also occurred at a maternally toxic dosage of 110 mg/kg/day. Developmental effects have not been identified in humans exposed to ritonavir during pregnancy nor has there been an association with cryptorchidism.

Use in Lactation

It is not known whether paritaprevir, ritonavir or ombitasvir, and their metabolites are excreted in human breast milk. Paritaprevir and its hydrolysis product M13, unchanged ombitasvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups.

Because of the potential for adverse reactions in nursing infants, breast feeding must be discontinued prior to initiation of treatment.

Paediatric Use

Safety and effectiveness of TECHNIVIE in children less than 18 years of age have not been established.

Use in the Elderly

No dose adjustment of TECHNIVIE is warranted in elderly patients. In Phase 3 clinical trials in genotype 1-infected patients, 8.5% (174/2053) of subjects were age 65 or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. The safety and effectiveness of TECHNIVIE has not been established in patients aged 70 years or over.

Genotoxicity

Paritaprevir

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).

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.

Ritonavir

Ritonavir showed no mutagenic potential in a series of assays for gene mutations (*S. typhimurium*, *E. coli* and mouse lymphoma cells) and chromosomal damage (mouse micronucleus assay *in-vivo* and human lymphocytes *in-vitro*).

Carcinogenicity

Paritaprevir/ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (300/30 mg/kg/day), resulting in paritaprevir and ritonavir AUC exposures approximately 56 and 6-fold higher, respectively than those in humans at the recommended dose of

150/50 mg. Similarly, paritaprevir/ritonavir was not carcinogenic in a 2-year rat study up to the highest dosage tested (300/30 mg/kg/day), resulting in paritaprevir/ritonavir AUC exposures approximately 14/6-fold higher than those in humans at 150/50 mg.

Two-year carcinogenicity studies have been conducted in rodents with ritonavir alone at dietary levels of 50, 100 and 200 mg/kg/day in mice, and 7, 15 and 30 mg/kg/day in rats. In male mice there was a dose-dependent increase in the incidence of hepatocellular adenomas, and adenomas and carcinomas combined, both reaching statistical significance only at the high-dose. In female mice there were small, statistically significant increases in these tumour incidences only at the high-dose. In rats, there were no tumorigenic effects.

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. Similarly, ombitasvir was not carcinogenic in a 2-year rat study up to the highest dose tested (30 mg per kg per day), resulting in ombitasvir exposures approximately 17-fold higher than those in humans at 25 mg.

Effect on Laboratory Tests

Serum ALT elevations

None of the 135 HCV GT4 infected subjects without cirrhosis and two (3%) of the 59 subjects with cirrhosis treated with TECHNIVIE experienced post-baseline serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment (see PRECAUTIONS).

Serum Bilirubin Elevations

Post-baseline elevations in bilirubin at least 2 times ULN were observed in 5% (7/134) of subjects receiving TECHNIVIE; all of whom were also receiving RBV. These bilirubin increases were predominately indirect and related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and possibly ribavirin-induced haemolysis. Bilirubin elevations occurred early after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were generally not associated with serum ALT elevations.

Anaemia/Decreased Haemoglobin

The mean change from baseline in haemoglobin levels in subjects treated with TECHNIVIE in combination with ribavirin was -2.1 g/dL and the mean change in subjects treated with TECHNIVIE alone was -0.4 g/dL. Decreases in haemoglobin levels occurred early in treatment (Week 1-2) with further reductions through Week 3. Haemoglobin values remained low during the remainder of treatment and returned towards baseline levels by post-treatment Week 4. One subject treated with TECHNIVIE with ribavirin had a single haemoglobin level decrease to less than 8 g/dL during treatment. Four percent (4/91) of subjects treated with TECHNIVIE with ribavirin underwent ribavirin dose reductions to manage anaemia/decreased haemoglobin levels; none received a blood transfusion or erythropoietin. No subjects treated with TECHNIVIE alone had a haemoglobin level less than 8 g/dL.

INTERACTIONS WITH OTHER MEDICINES

Also refer to the CONTRAINDICATIONS, PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES SECTION, Table 5 and PHARMACOKINETICS-Implications for Drug Interactions sections.

Recommendations for coadministration of TECHNIVIE for a number of medicinal products are provided in Table 5.

If a patient is already taking medicinal product(s) or initiating a medicinal product while receiving TECHNIVIE for which potential for a drug interaction is expected, dose adjustment of the concomitant medicinal product(s) or appropriate clinical monitoring should be considered (Table 5).

A change of 0.5- to 2.0-fold in the exposures (C_{max} and AUC) of paritaprevir and ombitasvir is not considered clinically relevant and does not require dose adjustment for TECHNIVIE.

If dose adjustments of concomitant medicinal products are made due to treatment with TECHNIVIE, doses should be re-adjusted after administration of TECHNIVIE is completed.

Table 5 provides the Least Squares Means Ratio (90% Confidence Interval) effect on the concentration of TECHNIVIE and concomitant medicinal products. Dose adjustment is not required for TECHNIVIE when co-administered with the concomitant medications listed in Table 5 unless otherwise noted.

The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC) in paritaprevir, ombitasvir and the co-administered medicinal product (\uparrow = increase (more than 20%), \downarrow = decrease (of more than 20%), \leftrightarrow = no change or change less than 20%).

Table 5: Interactions Between TECHNIVIE and Other Medicinal Products

Drug Class Drug Name	Effect	Clinical Comment		
Aminosalicylate				
Sulfasalazine	\uparrow sulfasalazine*	Mechanism: BCRP inhibition by paritaprevir and ritonavir. Caution should be used when sulfasalazine is coadministered with TECHNIVIE.		
Analgesic				
Paracetamol	No dose adjustments are required when co-administering with TECHNIVIE			
Angiotensin Receptor Blocker				
Valsartan, losartan, candesartan	\uparrow angiotensin receptor blockers	Mechanism: OATP1B inhibition by paritaprevir. Decrease the dose of the angiotensin receptor blockers and monitor patients for signs and symptoms of hypotension and/or worsening renal function.		
Antiarrhythmics				
Digoxin 0.5 mg single dose	\uparrow digoxin	Mechanism: P-gp inhibition by paritaprevir and ritonavir. Decrease digoxin dose by 30% - 50%. Appropriate		
	\leftrightarrow ombitasvir			
	C_{max}	AUC	C_{min}	
	1.58 (1.43-1.73)	1.36 (1.21-1.54)	1.24 (1.07-1.43)	
	0.99 (0.95-1.04)	1.02 (0.98-1.06)	1.01 (0.98-1.05)	

	↔ paritaprevir	1.15 (0.97-1.36)	1.12 (1.00-1.25)	0.97 (0.84-1.13)	monitoring of serum digoxin levels is recommended.
Bepridil*, lidocaine (systemic)*, disopyramide*, propafenone*	↑ antiarrhythmic agents Decrease in the dose and therapeutic concentration monitoring (if available) is recommended for the antiarrhythmic agents when co-administered with TECHNIVIE.				
Antibiotics					
Erythromycin*	↑ erythromycin				Mechanism: CYP3A4/P-gp inhibition by paritaprevir and ritonavir. Caution is advised when erythromycin is administered with TECHNIVIE.
Sulfamethoxazole	No dose adjustments are required when co-administering with TECHNIVIE				
Trimethoprim	No dose adjustments are required when co-administering with TECHNIVIE				
Anticancer Agents					
Imatinib*	↑ imatinib				Mechanism: BCRP inhibition by paritaprevir and ritonavir. Clinical monitoring and lower doses of imatinib are recommended.
Anticoagulants					
Warfarin 5 mg single dose	↔	C_{max} 0.96 (0.88-1.05)	AUC 0.87 (0.82-0.91)	C_{min} 0.87 (0.84-0.91)	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalised ratio (INR) is recommended.
	↔ R-warfarin	0.90 (0.82-0.99)	0.85 (0.76-0.95)	0.89 (0.84-0.93)	
	↔ S-warfarin	1.03 (0.95-1.11)	1.05 (0.99-1.11)	1.03 (0.98-1.09)	
	↔ Ombitasvir	1.15 (0.86-1.54)	1.11 (0.94-1.31)	0.99 (0.89-1.11)	
	↔ paritaprevir				
Fluindione	↑ fluindione				Appropriate monitoring of international normalised ratio (INR) is recommended.
Dabigatran etexilate*	↑ dabigatran				Mechanism: Intestinal P-gp inhibition by paritaprevir and ritonavir. TECHNIVIE may increase the plasma concentrations of dabigatran etexilate. Use with caution.
S-mephenytoin*	↓ S-mephenytoin				Mechanism: CYP2C19 induction by ritonavir. Clinical monitoring and dose adjustment may be needed for s-mephenytoin.
Antidepressants					
Escitalopram 10 mg single dose		C_{max} 0.92 (0.85-0.99)	AUC 0.75 (0.67-0.84)	C_{min} NA	No dose adjustment is necessary for escitalopram.
	↓ escitalopram				

	↔ S-desmethyl citalopram	1.17 (1.08-1.26)	1.07 (1.01-1.13)	NA	
	↔ ombitasvir	1.16 (1.09-1.23)	1.03 (1.00-1.06)	1.00 (0.97-1.03)	
	↔ paritaprevir	1.19 (0.84-1.68)	1.02 (0.82-1.27)	0.80 (0.71-0.89)	
Duloxetine 60 mg single dose		C_{max}	AUC	C_{min}	No dose adjustment is necessary for duloxetine.
	↔ duloxetine	0.83 (0.72-0.96)	0.80 (0.71-0.90)	NA	
	↔ ombitasvir	1.04 (0.92-1.16)	1.04 (1.00-1.09)	1.00 (0.97-1.03)	
	↔ paritaprevir	1.07 (0.63-1.81)	0.96 (0.70-1.32)	0.93 (0.76-1.14)	
Trazodone*	↑ trazodone				Mechanism: CYP3A4 inhibition by ritonavir. Trazodone should be used with caution and a lower dose of trazodone may be considered.
Antifungals					
Ketoconazole 400 mg once daily		C_{max}	AUC	C_{min}	When TECHNIVIE is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg per day.
	↑ ketoconazole	1.10 (1.05-1.16)	2.05 (1.93-2.18)	NA	
	↑ ombitasvir	0.98 (0.92-1.04)	1.26 (1.20-1.32)	NA	
	↑ paritaprevir	1.72 (1.32-2.26)	2.16 (1.76-2.66)	NA	
Voriconazole*	↓ voriconazole				Mechanism: CYP2C19 induction by ritonavir. Coadministration of TECHNIVIE with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
Antidiabetic					
Metformin	No dose adjustments are required when co-administering with TECHNIVIE. Concomitant metformin use in patients with renal insufficiency or hepatic impairment is not recommended.				
Antigout					
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 TECHNIVIE is required. See also the colchicine prescribing information. Use of colchicine is contraindicated with TECHNIVIE in patients with renal or hepatic impairment				
Antihistamines (for systemic use)					
Fexofenadine*	↑ fexofenadine				Mechanism: OATP1B1 inhibition by paritaprevir. Caution should be used when TECHNIVIE is coadministered with fexofenadine.
Calcium Channel Blockers					
Amlodipine ¹		C_{max}	AUC	C_{min}	Mechanism: CYP3A4

5 mg single dose	↑ amlodipine	1.26 (1.11-1.44)	2.57 (2.31-2.86)	NA	inhibition by ritonavir. The dose of amlodipine should be decreased by at least 50%. Clinical monitoring of patients is recommended.
	↔ 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)	
Diltiazem* Verapamil*	↑ diltiazem, verapamil ↑ paritaprevir*				Mechanism: CYP3A4/P-gp inhibition. Caution is advised due to the expected increase in paritaprevir exposures. Dose decrease and clinical monitoring of calcium channel blockers are recommended when coadministered with TECHNIVIE.
Nifedipine*	↑ nifedipine				Mechanism: CYP3A4 inhibition. Dose decrease and clinical monitoring of calcium channel blockers are recommended when coadministered with TECHNIVIE.
Contraceptives - Oral					
Norethisterone	No dose adjustments are required when co-administering with TECHNIVIE				
Diuretics					
Furosemide ¹ 20 mg single dose		C _{max}	AUC	C _{min}	Mechanism: Possibly due to UGT1A1 inhibition by paritaprevir and ombitasvir. Patients should be monitored for clinical effects; a decrease in furosemide dose of up to 50% may be required.
	↑ furosemide	1.42 (1.17-1.72)	1.08 (1.00-1.17)	NA	
	↔ ombitasvir	1.14 (1.03-1.26)	1.07 (1.01-1.12)	1.12 (1.08-1.16)	
	↔ paritaprevir	0.93 (0.63-1.36)	0.92 (0.70-1.21)	1.26 (1.16-1.38)	
HCV Antiviral					
Sofosbuvir	No dose adjustments are required when co-administering with TECHNIVIE				
HIV Antivirals: Protease Inhibitors					
Atazanavir 300 mg once daily (given at the same time)		C _{max}	AUC	C _{min}	Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir. In combination with ritonavir, the increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir and CYP3A by the additional dose of ritonavir. The recommended dose of atazanavir is 300 mg,
	↔ atazanavir	0.90 (0.83-0.97)	0.93 (0.85-1.02)	0.81 (0.72-0.91)	
	↔ ombitasvir	0.83 (0.74-0.94)	0.91 (0.81-1.02)	0.98 (0.87-1.11)	
	↑ paritaprevir	2.74 (1.76-4.27)	2.87 (2.08-3.97)	3.71 (2.87-4.79)	
Atazanavir/ritonavir ¹ 300/100 mg once daily (administered 12 hours apart from paritaprevir/ ritonavir/ombitasvir		C _{max}	AUC	C _{min}	
	↔ 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)	

)					without ritonavir, in combination with TECHNIVIE. Atazanavir must be administered at the same time as TECHNIVIE. Ritonavir dose in TECHNIVIE will provide atazanavir pharmacokinetic enhancement. Treatment with atazanavir/ritonavir + TECHNIVIE is not recommended.
Darunavir 800 mg once daily (given at the same time)		C_{max}	AUC	C_{min}	The recommended dose of darunavir is 800 mg once daily, without ritonavir, when administered at the same time as TECHNIVIE (ritonavir dose in TECHNIVIE will provide darunavir pharmacokinetic enhancement). This regimen can be used in the absence of extensive HIV protease inhibitor resistance (i.e., lack of darunavir resistance associated mutations [RAMS]). Darunavir combined with TECHNIVIE is not recommended in patients with extensive PI resistance.
	↔ darunavir	0.99 (0.92-1.08)	0.92 (0.84-1.00)	0.74 (0.63-0.88)	
	↔ ombitasvir	1.01 (0.87-1.17)	1.01 (0.91-1.11)	1.06 (0.99-1.13)	
↑ paritaprevir	2.09 (1.35-3.24)	1.94 (1.36-2.75)	1.85 (1.41-2.42)		
Darunavir/ritonavir ¹ 600/100 mg twice daily		C_{max}	AUC	C_{min}	
	↔ 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)	
Darunavir/ritonavir ¹ 800/100 mg once daily (administered 12 hours apart)		C_{max}	AUC	C_{min}	
	↑ 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)	
Lopinavir/ritonavir 400/100 mg twice daily ²		C_{max}	AUC	C_{min}	Mechanism: Increase in paritaprevir exposures may be due to inhibition of CYP3A/efflux transporters by lopinavir and a higher dose of ritonavir. Lopinavir/ritonavir 400/100 mg twice daily and 800/200 mg once daily (evening administration) increases paritaprevir concentrations. Lopinavir/ritonavir use is not recommended with TECHNIVIE.
	↔ lopinavir	1.06 (0.99-1.14)	1.13 (1.09-1.17)	1.34 (1.26-1.42)	
	↑ ombitasvir	1.07 (1.01-1.13)	1.25 (1.19-1.32)	1.48 (1.39-1.57)	
	↑ paritaprevir	4.76 (3.54-6.39)	6.10 (4.30-8.67)	12.33 (7.30-20.84)	
HIV Antivirals: Non-Nucleoside Reverse Transcriptase Inhibitors					
Rilpivirine ¹ 25 mg once daily administered in the		C_{max}	AUC	C_{min}	Mechanism: CYP3A4 inhibition by ritonavir. Coadministration of
	↑ rilpivirine	2.55 (2.08-3.12)	3.25 (2.80-3.77)	3.62 (3.12-4.21)	

morning, with food ³	↔ ombitasvir	1.11 (1.02-1.20)	1.09 (1.04-1.14)	1.05 (1.01-1.08)	TECHNIVIE with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine.
	↑ paritaprevir	1.30 (0.94-1.81)	1.23 (0.93-1.64)	0.95 (0.84-1.07)	
Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/300/200 mg once daily	Co-administration of efavirenz (enzyme inducer)-based regimens with paritaprevir and ritonavir resulted in ALT elevations and therefore, early discontinuation of the study.			Coadministration of efavirenz-based regimens with paritaprevir and ritonavir was poorly tolerated and resulted in liver enzyme elevations. (see CONTRAINDICATIONS).	
HIV Antivirals: Nucleoside reverse transcriptase inhibitors					
Lamivudine	No dose adjustments are required when co-administering with TECHNIVIE				
Abacavir	No dose adjustments are required when co-administering with TECHNIVIE				
HIV Antivirals: Integrase Strand Transfer Inhibitor					
Dolutegravir 50 mg once daily		C _{max}	AUC	C _{min}	No dose adjustment is necessary for dolutegravir.
	↑ dolutegravir	1.22 (1.15-1.29)	1.38 (1.30-1.47)	1.36 (1.19-1.55)	
	↔ ombitasvir	0.96 (0.89-1.03)	0.95 (0.90-1.00)	0.92 (0.87-0.98)	
	↔ paritaprevir	0.89 (0.69-1.14)	0.84 (0.67-1.04)	0.66 (0.59-0.75)	
Raltegravir 400 mg twice daily		C _{max}	AUC	C _{min}	No dose adjustment is necessary for raltegravir.
	↑ raltegravir	1.22 (0.78-1.89)	1.20 (0.74-1.95)	1.13 (0.51-2.51)	
No clinically relevant changes in paritaprevir and ombitasvir exposures (based on comparison with historical data) were observed during co-administration					
HIV ANTIVIRALS: Nucleoside Inhibitors					
Emtricitabine/Tenofovir disoproxil fumarate 200 mg once daily/300 mg once daily	↔ emtricitabine	0.94 (0.84-1.06)	1.07 (1.00-1.15)	1.25 (1.13-1.38)	No dose adjustment is necessary for emtricitabine/tenofovir.
	↔ tenofovir	0.80 (0.71-0.90)	1.01 (0.96-1.07)	1.13 (1.06-1.21)	
	↔ ombitasvir	0.97 (0.89-1.05)	1.00 (0.94-1.06)	1.02 (0.97-1.08)	
	↔ paritaprevir	1.02 (0.63-1.64)	1.04 (0.74-1.47)	1.09 (0.88-1.35)	
HMG-CoA Reductase Inhibitors					
Rosuvastatin 5 mg once daily		C _{max}	AUC	C _{min}	Mechanism: OATP1B inhibition by paritaprevir and BCRP inhibition by paritaprevir and ritonavir Rosuvastatin dose should not exceed 20 mg per day.
	↑ rosuvastatin	2.61 (2.01-3.39)	1.33 (1.14-1.56)	0.65 (0.57-0.74)	
	↔ ombitasvir	0.89 (0.81-0.97)	0.88 (0.83-0.92)	0.87 (0.83-0.91)	
Pravastatin 10 mg once daily		C _{max}	AUC	C _{min}	Mechanism: OATP1B/CYP3A4 inhibition by paritaprevir. Reduce pravastatin dose by 50%.
	↑ pravastatin	1.43 (1.09-1.88)	1.76 (1.46-2.13)	NA	
	↔ ombitasvir	0.98 (0.90-1.06)	0.94 (0.88-1.02)	0.97 (0.90-1.03)	

	↑ paritaprevir	1.44 (1.15-1.81)	1.33 (1.09-1.62)	1.28 (0.83-1.96)	
Immunosuppressants					
Cyclosporine 30 mg once daily single dose ⁴		C_{max}	AUC	C_{min}	When starting coadministration with TECHNIVIE, give one fifth of the total daily dose of ciclosporin once daily with TECHNIVIE. Monitor ciclosporin levels and adjust dose and/or dosing frequency as needed.
	↑ ciclosporin	0.83 (0.72-0.94)	4.28 (3.66-5.01)	12.85 (10.61- 15.55)	
	↔ ombitasvir	1.06 (1.02-1.11)	1.10 (1.07-1.12)	1.10 (1.06-1.14)	
	↑ paritaprevir	1.39 (1.10-1.75)	1.46 (1.29-1.64)	1.18 (1.08-1.30)	
Tacrolimus 2 mg single dose ⁵		C_{max}	AUC	C_{min}	Mechanism: Effect on tacrolimus is due to CYP3A4 inhibition by ritonavir. When starting coadministration with TECHNIVIE, administer 0.5 mg tacrolimus once every week. Monitor tacrolimus levels and adjust dose and/or dosing frequency as needed.
	↑ tacrolimus	4.27 (3.49-5.22)	85.81 (67.88- 108.49)	24.61 (19.69- 30.77)	
	↔ ombitasvir	0.94 (0.89-1.00)	0.95 (0.91-1.00)	0.95 (0.92-0.99)	
	↓ paritaprevir	0.71 (0.55-0.91)	0.79 (0.69-0.92)	0.84 (0.74-0.97)	
Insulin Secretagogues					
Repaglinide*	↑ repaglinide				Mechanism: OATP1B1 inhibition by paritaprevir. Caution should be used and dose decrease may be needed for repaglinide.
Muscle Relaxants					
Carisoprodol	↓ carisoprodol ↔ mepobramate (metabolite of carisoprodol)				No dose adjustment required; increase dose if clinically indicated
Cyclobenzaprine	↓ cyclobenzaprine ↓ norcyclobenzaprine (metabolite of cyclobenzaprine)				No dose adjustment required; increase dose if clinically indicated
Opioids					
Methadone 20-120 mg once daily ⁶		C_{max}	AUC	C_{min}	No dose adjustment is necessary for methadone.
	↔ R- methadone	0.94 (0.90-0.98)	0.97 (0.91-1.03)	0.99 (0.90-1.08)	
	↔ S- methadone	0.94 (0.90-0.99)	0.96 (0.89-1.03)	0.93 (0.84-1.02)	
	↔ ombitasvir and paritaprevir (based on the cross-study comparison)				
Buprenorphine/ naloxone 4-24 mg/1-6 mg once daily ⁶		C_{max}	AUC	C_{min}	No dose adjustment is necessary for buprenorphine/naloxone.
	↑ buprenorphi ne	1.19 (1.01-1.40)	1.51 (1.27-1.78)	1.65 (1.30-2.08)	
	↑ norbuprenor phine	1.82 (1.41-2.36)	2.11 (1.65-2.70)	1.87 (1.48-2.36)	
	↔ naloxone	0.99 (0.84-1.16)	1.11 (0.91-1.37)	NA	
	↔ ombitasvir and paritaprevir (based on the cross-study comparison)				

		comparison)			
Hydrocodone		C_{max}	AUC	C_{min}	Reduce the dose of hydrocodone by 50% and monitor patients for respiratory depression and sedation at frequent intervals. Upon completion of TECHNIVIE therapy, adjust the hydrocodone dose and monitor for signs of opioid withdrawal.
	↑ hydrocodone	1.27 (1.14-1.40)	1.90 (1.72-2.10)	NA	
	↔ ombitasvir	1.01 (0.93-1.10)	0.97 (0.93-1.02)	0.93 (0.90-0.97)	
	↔ paritaprevir	1.01 (0.80-1.27)	1.03 (0.89-1.18)	1.10 (0.97-1.26)	
Proton Pump Inhibitors					
Omeprazole 40 mg once daily		C_{max}	AUC	C_{min}	Mechanism: CYP2C19 induction by ritonavir. If clinically indicated, higher doses of omeprazole should be used.
	↓ omeprazole	0.48 (0.29-0.78)	0.46 (0.27-0.77)	NA	
	↔ ombitasvir	0.96 (0.81-1.14)	1.00 (0.88-1.12)	0.97 (0.89-1.07)	
	↔ paritaprevir	1.02 (0.64-1.62)	0.93 (0.64-1.34)	0.83 (0.67-1.04)	
Esomeprazole*, Lansoprazole*	↓ esomeprazole, lansoprazole				Mechanism: CYP2C19 induction by ritonavir. If clinically indicated, higher doses of esomeprazole/lansoprazole may be needed.
Sedatives/Hypnotics					
Triazolam, orally administered midazolam	Large ↑ triazolam and orally administered midazolam*				Triazolam and orally administered midazolam are extensively metabolised by CYP3A4. Co-administration of triazolam or orally administered midazolam with TECHNIVIE may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression. (see CONTRAINDICATIONS).
Zolpidem ¹ 5 mg single dose		C_{max}	AUC	C_{min}	No dose adjustment is necessary for zolpidem.
	↔ zolpidem	0.94 (0.76-1.16)	0.95 (0.74-1.23)	NA	
	↔ ombitasvir	1.07 (1.00-1.15)	1.03 (1.00-1.07)	1.04 (1.00-1.08)	
	↓ paritaprevir	0.63 (0.46-0.86)	0.68 (0.55-0.85)	1.23 (1.10-1.38)	
Alprazolam ¹ 0.5 mg single dose		C_{max}	AUC	C_{min}	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.
	↑ alprazolam	1.09 (1.03-1.15)	1.34 (1.15-1.55)	NA	
	↔ 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)	
Diazepam	↓ diazepam ↓ nordiazepam (metabolite of diazepam)				No dose adjustment required; increase dose if clinically indicated.
Thyroid Hormones					
Levothyroxine*	↑ levothyroxine				Mechanism: UGT1A1 inhibition by paritaprevir and ombitasvir. Clinical monitoring and dose adjustment may be required for levothyroxine.
<p>* Not studied; expected effect.</p> <ol style="list-style-type: none"> 1. Drug-drug interaction study carried out with paritaprevir/ritonavir/ombitasvir and dasabuvir combination. 2. Lopinavir/ritonavir 800/200 mg once daily (administered in the evening) was also administered with paritaprevir/ritonavir/ombitasvir + dasabuvir. The effect on C_{max} and AUC of the DAAs and lopinavir was similar to that observed when lopinavir/ritonavir 400/100 mg twice daily was administered with paritaprevir/ritonavir/ombitasvir + dasabuvir. 3. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food. 4. Ciclosporin 100 mg dosed alone and 10 mg administered with paritaprevir/ritonavir/ombitasvir. Dose-normalised ciclosporin ratios are shown for interaction with paritaprevir/ritonavir/ombitasvir. 5. Tacrolimus 2 mg dosed alone and 0.5 mg administered with paritaprevir/ritonavir/ombitasvir. Dose-normalized tacrolimus ratios are shown for interaction with paritaprevir/ritonavir/ombitasvir 6. Dose-normalised parameters reported for methadone, buprenorphine and naloxone. <p>Note: Doses used for TECHNIVIE were: paritaprevir 150 mg, ritonavir 100 mg and ombitasvir 25 mg once daily. TECHNIVIE was administered as multiple doses in all the drug interaction studies except the drug interaction studies with carbamazepine, gemfibrozil and ketoconazole.</p>					

ADVERSE EFFECTS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of TECHNIVIE cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of TECHNIVIE is based on data from three clinical studies in subjects with HCV genotype 4 infection. One study (PEARL-I) included 135 HCV genotype 4-infected subjects without cirrhosis, 91 who received paritaprevir 150 mg ritonavir 100 mg and ombitasvir 25 mg (administered as three paritaprevir 50 mg tablets, one ritonavir 100 mg capsule, and one ombitasvir 25 mg tablet) once daily with ribavirin for 12 weeks and 44 subjects who received paritaprevir 150 mg, ritonavir 100 mg and ombitasvir 25 mg once daily without ribavirin for 12 weeks. The second study (AGATE-I), included 60 subjects with compensated cirrhosis who received coformulated paritaprevir/ritonavir/ombitasvir (150/100/25 mg) once daily with ribavirin for 12 weeks. A third study (AGATE-II) included 131 HCV genotype 4-infected subjects in Egypt (100 without cirrhosis and 31 with compensated cirrhosis) who received coformulated paritaprevir/ritonavir/ombitasvir (150/100/25 mg) once daily with ribavirin for 12 weeks.

Table 6 includes rates of the adverse reactions from three trials that were conducted in HCV genotype 4-infected subjects who received paritaprevir/ritonavir/ombitasvir with and without ribavirin (PEARL-I, AGATE-I and AGATE-II). The majority of these events were mild in severity, none were serious and none led to discontinuation of treatment.

Table 6. Selected Adverse Reactions (All Grades) with ≥5% Frequency Reported in Subjects Treated with Paritaprevir , Ritonavir and Ombitasvir with or without Ribavirin for 12 Weeks

Adverse Reaction	PEARL-I (without cirrhosis)		AGATE-I (with cirrhosis)	AGATE-II (without cirrhosis)	AGATE-II (with cirrhosis)
	Paritaprevir + ritonavir + ombitasvir ^a + RBV 12 Weeks N = 91 %	Paritaprevir + ritonavir + ombitasvir ^a 12 Weeks N = 44 %	Paritaprevir + ritonavir + ombitasvir ^b + RBV 12 Weeks N = 60 %	Paritaprevir + ritonavir + ombitasvir ^b + RBV 12 Weeks N=100 %	Paritaprevir + ritonavir + ombitasvir ^b + RBV 12 Weeks N=31 %
Asthenia	29	25	18	3	0
Fatigue	15	7	17	35	29
Nausea	14	9	10	7	6
Insomnia	13	5	10	9	6
Pruritus [^]	7	5	8	23	13
Skin reactions [§] ,#	7	5	8	*	*
Anaemia	1	0	15	8	6

* Not calculated.

a. Administered as separate paritaprevir tablets, ritonavir capsules and ombitasvir tablets.

b. Administered as co-formulated tablets.

c. Grouped term 'pruritus' includes the preferred terms pruritus and pruritus generalized.

d. Grouped term 'skin reactions' includes the preferred terms rash, erythema, eczema, rash maculopapular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, rash generalized, dermatitis allergic, dermatitis contact, exfoliative rash, photosensitivity reaction, psoriasis, skin reaction, ulcer and urticaria.

e. The majority of events were graded as mild in severity. There were no serious events or severe cutaneous reactions, such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) or drug rash with eosinophilia and systemic symptoms (DRESS).

Post-Marketing Adverse Reactions

The following adverse reactions have been identified during post approval use of paritaprevir/ritonavir/ombitasvir with and without dasabuvir. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity reactions (including tongue and lip swelling) have been observed (see CONTRAINDICATIONS).

Hepatobiliary Disorders: Hepatic decompensation and hepatic failure have been observed (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Recommended Dose in Adults

The recommended oral dose of TECHNIVIE is two paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets once daily (in the morning) with a meal without regard to fat or calorie content (*see PHARMACOLOGY*)

Patients should be instructed to swallow the tablets whole (i.e. patients should not chew, break or dissolve the tablets).

TECHNIVIE is used in combination with ribavirin. When administered with TECHNIVIE, the recommended dosage of RBV is based on weight: 1000 mg per day for subjects less than 75 kg and 1200 mg per day for those weighing at least 75 kg, divided and administered twice-daily with food. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

Table 7 shows the recommended TECHNIVIE treatment regimen and duration for HCV genotype 4 patients.

Table 7. Treatment Regimen and Duration for Patients with HCV Genotype 4

Patient Population	Treatment	Duration
Genotype 4 without cirrhosis	TECHNIVIE + ribavirin*	12 weeks
Genotype 4 with compensated cirrhosis	TECHNIVIE + ribavirin	12 weeks

*TECHNIVIE administered without RBV for 12 weeks may be considered for treatment-naïve patients without cirrhosis who cannot take or tolerate ribavirin (see CLINICAL TRIALS).

TECHNIVIE should be taken as directed for the prescribed duration, without interruption.

Missed Dose

Inform patients that in case a dose of paritaprevir, ritonavir, ombitasvir is missed, the prescribed dose can be taken within 12 hours.

If more than 12 hours has passed since paritaprevir, ritonavir, ombitasvir is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.

Use in Special Populations

Hepatic Impairment

No dose adjustment of TECHNIVIE is required in patients with mild hepatic impairment (Child-Pugh A). TECHNIVIE is not recommended in patients with moderate hepatic impairment (Child-Pugh B). A decision to initiate treatment in patients with Child-Pugh B should be guided by assessment of the potential benefits and risks for the individual. TECHNIVIE is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS and PRECAUTIONS).

Renal Impairment

Based on the pharmacokinetic data in HCV uninfected subjects (n=24), no dose adjustment of TECHNIVIE is recommended in subjects with mild, moderate or severe renal impairment. The

efficacy and safety of TECHNIVIE have not been evaluated in HCV-infected subjects with moderate or severe renal impairment. TECHNIVIE has not been studied in patients on dialysis.

OVERDOSAGE

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. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately.

For information on the management of overdose in Australia contact the Poison Information Centre on 131126 and in New Zealand call 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets are pink-coloured, film-coated, oblong biconvex shaped, debossed with "AV1" on one side.

TECHNIVIE is dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each daily dose pack contains two 75 mg/50 mg/12.5 mg paritaprevir/ritonavir/ombitasvir tablets.

Storage Conditions

Store below 30°C in a dry place.

NAME AND ADDRESS OF THE SPONSOR

AbbVie Pty Ltd
Level 7, 241 O'Riordan Street
Mascot NSW 2020
Australia

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

30 November 2016