PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTECHNIVIE™

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

Antiviral Agent

Date of Preparation:
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[Pr]TECHNIVIE

ombitasvir/paritaprevir/ritonavir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients[a]
oral	ombitasvir/paritaprevir /ritonavir film-coated tablets: 12.5/75/50 mg	None

a. For a complete listing see ***DOSAGE FORMS, COMPOSITION AND PACKAGING*** section.

INDICATIONS AND CLINICAL USE

TECHNIVIE (ombitasvir/paritaprevir/ritonavir) tablets with ribavirin is indicated for the treatment of adults with genotype 4 chronic hepatitis C virus infection, including those with compensated cirrhosis, who are either treatment naïve or previously treated with peginterferon and ribavirin.

The following point should be considered when initiating treatment with TECHNIVIE:

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

Geriatrics (> 65 years of age):

No overall differences in safety and efficacy have been observed in patients younger than 65 or older than 65 (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Pediatrics (< 18 years of age):

Safety and effectiveness of TECHNIVIE in children less than 18 years of age have not been established (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

- Patients who are hypersensitive to the medicinal ingredients of TECHNIVIE (ombitasvir, paritaprevir and ritonavir) or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

- Patients with known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome).

- When TECHNIVIE is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen (see the ribavirin Product Monograph).

- The use of ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant, may be pregnant, or plan to become pregnant because of the risks for birth defects and fetal death associated with ribavirin (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pregnant Women**).

- Patients with moderate to severe hepatic impairment (Child-Pugh B and C) due to risk of potential toxicity.

- The following categories of drugs are contraindicated with TECHNIVIE (see **Table 1**):

    - Drugs for which elevated plasma concentrations are associated with serious and/or life-threatening events and that are sensitive cytochrome P450 (CYP) 3A substrates;

    - Drugs that are moderate or strong inducers of CYP3A that may lead to reduced efficacy of TECHNIVIE.

Table 1. Drugs that Are Contraindicated with TECHNIVIE

Drug Class	Drug Name
Alpha1-adrenoreceptor antagonist	alfuzosin HCl
Antiarrhythmic	dronedarone
Antibiotic	fusidic acid (oral formulation)*
Anticonvulsants	carbamazepine, phenytoin, phenobarbital
Antigout	colchicine, in patients with renal and/or hepatic impairment
Antihistamine	astemizole, terfenadine
Antimycobacterial	rifampin
Antipsychotic	lurasidone
Antiviral	efavirenz-containing regimens, including Atripla, etravirine, nevirapine

Drug Class	Drug Name
Endothelin receptor agonist	bosentan
Ergot derivatives	ergotamine, dihydroergotamine, ergonovine*, methylergonovine*
GI Motility Agent	cisapride*
Herbal Product	St. John's Wort *(Hypericum perforatum)*
Hormonal Product	ethinyl estradiol-containing medications such as combined oral contraceptives
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin
Long-acting beta-adrenoceptor agonist	salmeterol
Neuroleptics	pimozide
PDE5 enzyme inhibitor	sildenafil only when used for the treatment of pulmonary arterial hypertension (PAH)
Sedatives/hypnotics	oral midazolam, triazolam
Others	modafinil

* Drugs not sold in Canada.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Potential for Hepatitis B virus (HBV) reactivation:** Screen all patients for evidence of current or prior HBV infection before initiating TECHNIVIE therapy. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct-acting HCV antivirals (DAAs) in patients co-infected with HBV. (See **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**)

General

When TECHNIVIE (ombitasvir/paritaprevir/ritonavir) is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, also apply to this combination regimen (see the ribavirin Product Monograph).

TECHNIVIE contains ritonavir and should not be co-administered with additional ritonavir or ritonavir-containing regimens.

As a fixed dose combination formulation, no dosage adjustments for TECHNIVIE are possible.

Retreatment of patients previously treated with TECHNIVIE or other direct-acting antiviral (DAA) agents is not recommended since the efficacy in these patients has not been established.

Transaminase Elevations with Concomitant Drugs

Clinically significant transaminase elevations were observed when ombitasvir, paritaprevir, ritonavir and dasabuvir were co-administered with efavirenz- or ethinyl estradiol-containing regimens and therefore these drugs are contraindicated with TECHNIVIE (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Table 5**). When TECHNIVIE is co-administered with other drugs known to cause elevations of transaminases, caution should be exercised and monitoring of transaminase levels should be considered. If transaminase elevations occur, consideration should be given to whether the other drug may be discontinued. Discontinuation of TECHNIVIE should be considered if there are clinical signs of liver inflammation that are accompanied by persistent elevations in ALT, direct bilirubin or international normalized ratio (INR) (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic, ALT Elevations**).

Use with Tacrolimus

Co-administration of TECHNIVIE with systemic tacrolimus increases the concentrations of tacrolimus via CYP3A inhibition (see **DRUG INTERACTIONS**, **Table 9**). Serious and/or life threatening adverse events have been observed with co-administration of TECHNIVIE with systemic tacrolimus. Avoid concomitant use of tacrolimus with TECHNIVIE unless the benefits outweigh the risks.

If tacrolimus and TECHNIVIE are used concomitantly, tacrolimus should not be administered on the day TECHNIVIE is initiated. Beginning the day after TECHNIVIE is initiated reinitiate tacrolimus at a reduced dose based on tacrolimus whole blood concentrations. The recommended tacrolimus dose is 0.5 mg every 7 days (see **DRUG INTERACTIONS**, **Table 6**).

Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with TECHNIVIE and the dose and/or dosing frequency should be adjusted as needed. Patients should be monitored frequently for any changes in renal function or tacrolimus-associated adverse events. Refer to the tacrolimus Product Monograph for additional dosing and monitoring instructions.

Use with Fluticasone (and other glucocorticoids metabolized by CYP3A)

Use caution when administering TECHNIVIE with fluticasone or other glucocorticoids that are metabolized by CYP3A4 (see **DRUG INTERACTIONS, Table 7**). Concomitant use of inhaled glucocorticoids metabolized by 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, a CYP3A4 substate, is not recommended due to expected increases in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose and monitor for quetiapine-associated adverse reactions (see **DRUG INTERACTIONS**, **Table 6** and the quetiapine Product Monograph for the recommendations on adverse reaction monitoring).

Use with Rilpivirine

Concomitant use of ombitasvir, paritaprevir, ritonavir and dasabuvir with rilpivirine, a CYP3A4 substrate, significantly increased rilpivirine exposure by 243%. Co-administration of TECHNIVIE with rilpivirine is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine (see **DRUG INTERACTIONS**,**Table 6**).

Use with HMG-CoA Reductase Inhibitors

Simvastatin and lovastatin are contraindicated with TECHNIVIE. Concomitant use of atorvastatin with TECHNIVIE should be avoided; for patients receiving fluvastatin use the lowest dose or switch to low-dose pravastatin or rosuvastatin (see **DRUG INTERACTIONS**, **Table 5** and **Table 7**).

Hepatic/Biliary/Pancreatic

Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis:

Hepatic decompensation and hepatic failure, including liver transplants or fatal outcomes, have been reported from postmarketing sources in patients treated with TECHNIVIE 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 characterized by the acute onset of 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. Discontinue treatment in patients who develop evidence of hepatic decompensation.

TECHNIVIE is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C).

For patients with cirrhosis:

- Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal hemorrhage).

- Hepatic laboratory testing including direct bilirubin levels should be performed at baseline and during the first 4 weeks of starting treatment and as clinically indicated.

- Discontinue TECHNIVIE in patients who develop evidence of hepatic decompensation.

ALT Elevations

During clinical trials with ombitasvir, paritaprevir and ritonavir with or without 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 patients (see **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**, **Laboratory Abnormalities**). **These ALT elevations were significantly more frequent in female patients who were using ethinyl estradiol-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 ombitasvir, paritaprevir and ritonavir with or without 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.

During clinical trials with ombitasvir, paritaprevir and ritonavir with dasabuvir, patients using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any estrogens (1%). However, due to the limited number of patients taking these other estrogens (n=87) in clinical trials, caution is warranted for co-administration with TECHNIVIE.

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, as well as later signs such as jaundice and discolored feces. If elevated liver chemistries are identified, careful follow-up is recommended. Consider discontinuing TECHNIVIE if ALT levels remain persistently greater than 10 times the ULN. TECHNIVIE should be discontinued if there are clinical signs of liver inflammation that are accompanied by persistent elevations in ALT, conjugated bilirubin, alkaline phosphatase, direct bilirubin or international normalized ratio (INR).

Potential for Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV–coinfected patients who were undergoing, or completed treatment with DAA. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patient with serologic evidence of resolved HBV infection (i.e. HBsAg negative and anti-HBc positive)

should be monitored and treated according to current clinical practice guidelines to manage potential for HBV reactivation (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Renal Impairment

No dose adjustment of TECHNIVIE is required in patients with mild, moderate or severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Insufficiency**).

TECHNIVIE has not been studied in patients on dialysis.

Since TECHNIVIE is administered with ribavirin, refer to the ribavirin Product Monograph for information regarding use in patients with renal impairment.

Sexual Function/Reproduction

Fertility

There are no studies on the effect of TECHNIVIE on human fertility.

No effects on fertility were observed in animal studies with the components of TECHNIVIE (see **NON-CLINICAL TOXICOLOGY**, **Fertility**).

Use with Ribavirin in Females and Males of Reproductive Potential

Ribavirin may cause birth defects and/or death of the exposed fetus (see **CONTRAINDICATIONS**). Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients when TECHNIVIE is administered in combination with ribavirin as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin.

TECHNIVIE in combination with ribavirin should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use at least two effective forms of contraception during treatment and for at least 6 months after treatment has concluded. See additional information on specific hormonal contraceptives in **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**, **ALT Elevations;** and **DRUG INTERACTIONS**, **Table 7**. Routine monthly pregnancy tests must be performed during this time (see the ribavirin Product Monograph).

Special Populations

Pregnant Women

When TECHNIVIE is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin Product Monograph for more information on use in pregnancy. See additional information on specific hormonal contraceptives in **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**, **ALT Elevations;** and **DRUG INTERACTIONS**, **Table 7**.

There are no studies with TECHNIVIE in pregnant women.

No effects on embryo-fetal development have been noted in studies in animals with paritaprevir/ritonavir, 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) the exposures in humans at the recommended clinical dose. For ombitasvir, the highest dose tested produced exposures equal to 28-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.

Ombitasvir and paritaprevir were minimally transferred through the placenta of pregnant rats.

Nursing Women

It is not known whether paritaprevir/ritonavir, 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. A risk to the newborn cannot be excluded; therefore nursing must be discontinued prior to initiation of treatment with TECHNIVIE. Physicians prescribing ribavirin should also refer the patient to the Product Monograph for ribavirin.

Pediatrics (< 18 years of age)

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

Geriatrics (> 65 years of age)

No dose adjustment of TECHNIVIE is needed in geriatric patients. In the clinical trials PEARL-I and AGATE-I, 7.0% (14/195) of patients were at least 65 years of age. In Phase 3 clinical trials of ombitasvir, paritaprevir and ritonavir plus dasabuvir, 8.5% (174/2053) of patients were at least 65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

HCV-HBV Co-infection

The safety and efficacy of TECHNIVIE have not been established in HCV patients co-infected with HBV. HBV reactivation has been reported during treatment and post-treatment with DAAs in patients co-infected with HBV who were not undergoing treatment for HBV infection (see **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**).

HCV-HIV Co-infection

The safety and efficacy of TECHNIVIE have not been established in patients co-infected with HIV. The ritonavir component of TECHNIVIE is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with TECHNIVIE should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

TECHNIVIE is contraindicated with efavirenz-containing regimens (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**, **Table 5)**.

Drug interactions should be taken into account when treating HIV-co-infection (see **DRUG INTERACTIONS**).

Post-Liver Transplant

The safety and efficacy of TECHNIVIE have not been established in post liver transplant patients.

Use in Patients Who Have Failed Previous Therapy with Direct-Acting Antivirals against HCV

TECHNIVIE efficacy has not been studied in patients who have previously failed therapy with other DAA agents.

Monitoring and Laboratory Tests

Refer to **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**, **Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis** for additional information.

Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV coinfected. Co-infected patients should be monitored for clinical and laboratory signs (e.g. HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

TECHNIVIE should be administered with ribavirin (RBV). Refer to the ribavirin Product Monograph for a list of ribavirin-associated adverse reactions.

The safety assessment of TECHNIVIE is based on data from two clinical trials in HCV genotype 4-infected patients. One study (PEARL-I) included 91 patients without cirrhosis (treatment naïve or pegIFN/RBV-experienced) who received ombitasvir, paritaprevir and ritonavir with ribavirin for 12 weeks and 126 patients (of which 82 were genotype 1b-infected and either treatment naïve or null responders to previous pegIFN/RBV treatment and 44 were genotype 4-infected and treatment naïve) without cirrhosis who received ombitasvir, paritaprevir and ritonavir without ribavirin for 12 weeks. The other study (AGATE-I), included 60 patients with compensated cirrhosis (treatment naïve or pegIFN/RBV-experienced) who received TECHNIVIE coformulated tablets once daily with ribavirin for 12 weeks and 60 subjects who received TECHNIVIE coformulated tablets once daily with ribavirin for 16 weeks.

In patients receiving ombitasvir, paritaprevir and ritonavir with ribavirin, the most commonly reported treatment emergent adverse events considered related to study drug by site investigator (greater than 10% of patients) were asthenia, fatigue, and headache. No patient permanently discontinued treatment due to a related adverse event and no patient had a treatment interruption due to a related adverse event.

In patients receiving ombitasvir, paritaprevir and ritonavir without ribavirin, the most commonly reported treatment emergent adverse events considered related to study drug by site investigator (greater than 10% of patients) were asthenia and headache. No patient permanently discontinued treatment due to a related adverse event and one patient had a treatment interruption due to a related adverse event.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The adverse drug reactions of at least moderate intensity (Grades 2 to 4) and considered at least possibly or related to treatment and occurring at a frequency of ≥ 2% in clinical trials of TECHNIVIE are presented in **Table 2**.

The majority of adverse events in the PEARL-I and AGATE-I clinical trials were of grade 1 severity. The safety profile of ombitasvir, paritaprevir and ritonavir with ribavirin was consistent with the known safety profile of ombitasvir, paritaprevir, ritonavir with dasabuvir and ribavirin in patients with HCV genotype 1 infection in Phase 3 clinical trials.

Table 2. Tabulation of Adverse Reactions* of at Least Moderate Intensity (Grade 2 – 4) in ≥ 2% of Patients in PEARL-I or AGATE-I

	PEARL-I		AGATE-I	
Adverse Reaction	**Ombitasvir, paritaprevir, ritonavir + RBV 12 Weeks N = 91 n (%)**	**Ombitasvir, paritaprevir, ritonavir 12 Weeks N = 126 n (%)**	**Ombitasvir, paritaprevir, ritonavir + RBV 12 Weeks N = 60 n (%)**	**Ombitasvir, paritaprevir, ritonavir + RBV 16 Weeks N = 60 n (%)**
Headache	3 (3.3)	3 (2.4)	0	2 (3.3)
Pruritus	3 (3.3)	0	0	0
Asthenia	2 (2.2)	1 (0.8)	1 (1.7)	2 (3.3)
Hyperbilirubinaemia	2 (2.2)	0	0	0
Insomnia	2 (2.2)	1 (0.8)	0	0
Fatigue	1 (1.1)	3 (2.4)	0	4 (6.7)

* Frequencies of adverse events are based on treatment-emergent adverse events considered at least possibly related to study drug by site investigators.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Treatment emergent adverse events (Grades 2 to 4) considered at least possibly related to study drug by site investigators which occurred in less than 2% of patients in the PEARL-I and AGATE-I clinical trials are listed below by system organ class (**Table 3**).

Table 3. Adverse Reactions (Grade 2 – 4) in < 2% of Patients in PEARL-I and AGATE-I

Body System	Adverse Events
Blood and lymphatic system disorders:	anaemia, thrombocytopenia
Gastrointestinal disorders:	abdominal pain, aphthous stomatitis, diarrhoea, dyspepsia, nausea
General disorders and administration site conditions:	chills, drug withdrawal syndrome, irritability, oedema peripheral, peripheral swelling
Investigations:	alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, haemoglobin decreased, international normalised ratio abnormal
Metabolism and nutrition disorders:	decreased appetite, gout, hyperglycaemia
Musculoskeletal and connective tissue disorders:	arthralgia, muscle spasms, myalgia, pain in extremity
Nervous system disorders:	disturbance in attention, dizziness, memory impairment
Psychiatric disorders:	abnormal dreams, anhedonia, anxiety, depression, libido decreased
Respiratory, thoracic and mediastinal disorders:	dyspnoea exertional, epistaxis
Skin and subcutaneous tissue disorders:	dry skin, eczema dry skin, eczema, rash

Treatment emergent adverse event of jaundice (Grade 1) considered at least possibly related to TECHNIVIE with or without ribavirin by site investigators occurred at a frequency of ≥ 2% of patients in AGATE-I (3.3% for each treatment duration) and in no patients in PEARL-I.

Treatment emergent adverse event of ocular icterus (Grade 1) considered at least possibly related to TECHNIVIE with or without ribavirin by site investigators occurred at a frequency of < 2% of patients in AGATE-I and in no patients in PEARL-I.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

Changes in selected laboratory parameters are described in**Table 4**.

Table 4. Selected Treatment Emergent Laboratory Abnormalities of at Least Moderate Intensity (Grades 2-4) in Studies PEARL-I and AGATE-I

Laboratory Parameters	PEARL-I		AGATE-I	
	Ombitasvir, paritaprevir, ritonavir + RBV 12 Weeks N = 91 %	Ombitasvir, paritaprevir, ritonavir 12 Weeks N = 126[a] %	Ombitasvir, paritaprevir, ritonavir + RBV 12 Weeks N = 60[b] %	Ombitasvir, paritaprevir, ritonavir + RBV 16 Weeks N = 60 %
ALT				
> 5-20 × ULN* (Grade 3)	0	1.6[c]	3.4	0
> 20 × ULN (Grade 4)	0	0	0	0
Hemoglobin				
< 10-8 g/dL (Grade 2)	2.2	0.8	10.2	18.3
< 8-6.5 g/dL (Grade 3)	1.1	0	0	1.7
< 6.5 g/dL (Grade 4)	0	0	0	0
Total Bilirubin				
> 3-10 × ULN (Grade 3)	3.3	0	8.5	5.0
> 10 × ULN (Grade 4)	0	0	0	0

* ULN: Upper Limit of Normal according to testing laboratory.

a. Percentages were based on 125 patients with post-baseline values for the respective parameters.

b. Percentages were based on 59 patients with post-baseline values for the respective parameters.

c. ALT elevations were asymptomatic, occurred during the first 4 weeks of treatment and resolved while continuing therapy.

Serum ALT Elevations

During clinical trials with ombitasvir, paritaprevir and ritonavir with or without dasabuvir and with and without ribavirin, less than 1% of patients who were not on ethinyl estradiol-containing medications experienced transient serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. These elevations were asymptomatic, generally occurred during the first 4 weeks of treatment and resolved with ongoing therapy. Increases in ALT were not associated with simultaneous increases in bilirubin levels. No specific monitoring of liver chemistries is required for the majority of patients (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**, **ALT Elevations**).

Serum Bilirubin Elevations

Transient elevations in bilirubin (predominantly indirect) were observed in patients receiving ombitasvir, paritaprevir and ritonavir with or without dasabuvir and with ribavirin, related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced hemolysis. 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 patients who did not receive ribavirin.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post approval use of TECHNIVIE. 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 angioedema).

Hepatobiliary Disorders: Hepatic decompensation, hepatic failure (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).

DRUG INTERACTIONS

Overview

Drug interaction studies were conducted with a combination of the individual components of TECHNIVIE (ombitasvir + paritaprevir + ritonavir) with or without dasabuvir or with co-formulated products (ombitasvir + paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir) with or without dasabuvir.

Drug-Drug Interactions

Potential for TECHNIVIE to Affect Other Drugs

Paritaprevir is an inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3, and paritaprevir and ritonavir are inhibitors of OATP2B1. Paritaprevir and ritonavir are inhibitors of P-gp, BCRP *in vivo*. Paritaprevir and ombitasvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of cytochrome P450 (CYP) 3A4. Drugs that are primarily metabolized by CYP3A, or are substrates of UGT1A1, BCRP, OATP1B1, OATP1B3 or OATP2B1 may have significantly increased plasma concentrations when co-administered with TECHNIVIE.

While ritonavir alone is shown to induce multiple CYPs (cytochrome P450) *in vitro*, TECHNIVIE does not significantly affect CYP2C9 at clinically relevant concentrations. In addition, TECHNIVIE is not expected to inhibit CYP2D6 and a clinically significant increase in exposures of CYP2D6 substrates is not expected during co-administration with TECHNIVIE. However, co-administration of TECHNIVIE can decrease exposures of drugs that are primarily metabolized by CYP2C19 (e.g., omeprazole) and clinical monitoring and/or dose increases might be needed for these substrates.

Paritaprevir, ombitasvir and ritonavir do not inhibit organic anion transporter (OAT1) *in vivo* and are not expected to inhibit organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations; therefore TECHNIVIE does not affect these active renal elimination pathways.

Paritaprevir, ombitasvir and ritonavir are not expected to inhibit organic cation transporter 1 (OCT1) at clinically relevant concentrations.

Potential for Other Drugs to Affect TECHNIVIE

Paritaprevir and ritonavir are primarily metabolized by CYP3A.

Strong inhibitors of CYP3A may significantly increase paritaprevir and ritonavir exposures when co-administered with TECHNIVIE.

Drugs that induce CYP3A are expected to decrease paritaprevir, ombitasvir and ritonavir plasma concentrations significantly and reduce their therapeutic effect.

Drugs that are moderate or strong CYP3A inducers are contraindicated with TECHNIVIE (see **CONTRAINDICATIONS**).

Ombitasvir, paritaprevir and ritonavir are substrates of P-gp. Paritaprevir is a substrate of BCRP, OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may increase exposures of the various components of TECHNIVIE.

Paritaprevir is a substrate of CYP3A and transport proteins. Caution is advised if co-administering TECHNIVIE with products that are both moderate inhibitors of CYP3A4 and inhibitors of multiple transporters (P-gp, BCRP and/or OATP1B1/ OATP1B3) as it can result in clinically relevant increases in paritaprevir exposures.

Drugs that Are Contraindicated with TECHNIVIE

The drugs that are contraindicated with TECHNIVIE are listed in **Table 5**.

Table 5. Drugs that Are Contraindicated with TECHNIVIE

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ALPHA1-ADRENORECEPTOR ANTAGONISTS		
alfuzosin HCL	CYP3A inhibition by ritonavir	Potential for increased alfuzosin concentrations which can result in hypotension.
ANTIARRHYTHMICS		
dronedarone	CYP3A inhibition by ritonavir	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
ANTIBIOTICS		
fusidic acid (oral formulation)*	CYP3A4 inhibition by ritonavir	Potential for increased fusidic acid concentrations with risk of adverse events such as hepatotoxicity.
ANTICONVULSANTS		
carbamazepine, phenytoin, phenobarbital	CYP3A4 induction by carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
ANTIGOUT		
colchicine	CYP3A4 inhibition by ritonavir	Contraindicated in patients with renal or hepatic impairment. For recommendations concerning patients with normal renal and hepatic function see **Table 7**.
ANTIHISTAMINES		
astemizole, terfenadine	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias.
ANTIMYCOBACTERIALS		

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
rifampin	CYP3A4/CYP2C8 induction by rifampin	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
ANTIPSYCHOTICS		
lurasidone	CYP3A inhibition by ritonavir	Potential for serious and/or life-threatening reactions.
ENDOTHELIN RECEPTOR ANTAGONISTS		
bosentan	CYP3A4 induction by bosentan	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
ERGOT DERIVATIVES		
ergotamine, dihydroergotamine, ergonovine*, methylergonovine*	CYP3A4 inhibition by ritonavir	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
GI MOTILITY AGENTS		
cisapride*	CYP3A4 inhibition by ritonavir	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
HERBAL PRODUCTS		
St. John's Wort *(Hypericum perforatum)*	CYP3A4 induction by St. John's Wort	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
HIV-ANTIVIRAL AGENTS		
efavirenz-containing regimens, such as Atripla		Co-administration of efavirenz-based regimen with paritaprevir and ritonavir containing regimen was poorly tolerated and resulted in liver enzyme elevations and early study termination.
etravirine, nevirapine	CYP3A4 induction by etravirine or nevirapine	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
HORMONAL PRODUCTS		
ethinyl estradiol-containing drugs (combined oral contraceptives, contraceptive vaginal rings, contraceptive patch)	possibly due to UGT inhibition by ombitasvir and paritaprevir	Potential for ALT elevations.
HMG CoA REDUCTASE INHIBITORS		
lovastatin, simvastatin	CYP3A4 and OATP1B inhibition by ritonavir and paritaprevir, respectively	Potential for serious reactions such as myopathy including rhabdomyolysis.
LONG-ACTING BETA-ADRENOCEPTOR AGONISTS		
salmeterol	CYP3A4 inhibition by ritonavir	Potential for QT prolongation, palpitations and sinus tachycardia.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
NEUROLEPTICS		
Pimozide	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias.
PDE5 ENZYME INHIBITORS		
sildenafil only at the doses used daily for the treatment of pulmonary arterial hypertension	CYP3A4 inhibition by ritonavir	Potential for visual disturbances, hypotension, priapism, and syncope.
SEDATIVES/HYPNOTICS		
oral midazolam, triazolam	CYP3A4 inhibition by ritonavir	Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
OTHER		
modafinil	CYP3A4 induction by modafinil	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.

* Drugs not sold in Canada

Drugs that Should not be Co-administered with TECHNIVIE

The drugs that should not be co-administered with TECHNIVIE are listed in **Table 6**.

Table 6. Drugs that Should not be Co-administered with TECHNIVIE

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ANTIARRHYTHMICS		
amiodarone, disopyramide, flecainide, lidocaine (systemic), propafenone, quinidine	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias. Physicians considering combined therapy of TECHNIVIE with amiodarone should refer to the amiodarone Product Monograph, carefully weigh the potential benefits and risks, and monitor patients for amiodarone-associated adverse reactions.
ANTIPSYCHOTICS		
quetiapine	CYP3A4 inhibition by ritonavir	Potential for an increase in quetiapine exposure. If the co-administration is necessary, reduce the quetiapine dose and closely monitor patients for quetiapine-associated adverse reactions (see the quetiapine Product Monograph).
HIV-ANTIVIRAL AGENTS		
rilpivirine	CYP3A4 inhibition by ritonavir	Potential for QT interval prolongation due to increased rilpivirine exposure.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ritonavir and ritonavir-containing regimens, including atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir	CYP3A4 inhibition by ritonavir	Potential for an increase in paritaprevir exposures. For administration of TECHNIVIE with atazanavir or darunavir without additional ritonavir, refer to **Table 7**.
IMMUNOSUPPRESSANTS		
everolimus	CYP3A4 inhibition by ritonavir	Should not be co-administerered due to a significant increase in everolimus exposures that cannot be properly dose-adjusted with available dose strengths.
sirolimus	CYP3A4 inhibition by ritonavir	Increase in sirolimus exposure (see **Table 9**) for which no adequate dose adjustment recommendations can be provided.
tacrolimus	CYP3A4 inhibition by ritonavir	Co-administration of TECHNIVIE with systemic tacrolimus increases the concentrations of tacrolimus via CYP3A inhibition (see **Table 9**). Serious and/or life threatening adverse events have been observed with co-administration of TECHNIVIE with systemic tacrolimus. Avoid concomitant use of tacrolimus with TECHNIVIE unless the benefits outweigh the risks. If tacrolimus and TECHNIVIE are used concomitantly, tacrolimus should not be administered on the day TECHNIVIE is initiated. Beginning the day after TECHNIVIE is initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. The recommended tacrolimus dosing is 0.5 mg every 7 days (see **WARNINGS AND PRECAUTIONS**). Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with TECHNIVIE and the dose and/or dosing frequency should be adjusted as needed. Upon completion of TECHNIVIE treatment, the appropriate dose and dosing frequency of tacrolimus should be guided by assessment of tacrolimus blood concentrations.
OPIOID ANALGESICS		
alfentanil, fentanyl	CYP3A4 inhibition by ritonavir	Should not be co-administered since these drugs are CYP3A substrates and their exposures may increase during co-administration with TECHNIVIE.

Established and Other Potential Drug Interactions

Table 7 provides the effect of co-administration of TECHNIVIE on concentrations of concomitant drugs and effects of other drugs on TECHNIVIE.

Table 7. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of TECHNIVIE and/or Concomitant Drug	Clinical comments
ANGIOTENSIN RECEPTOR BLOCKERS		
candesartan, losartan and valsartan	↑ candesartan ↑ losartan ↑ valsartan	Decrease the dose of the angiotensin receptor blockers and monitor patients.
ANTIARRHYTHMICS		
digoxin	↑ digoxin	Decrease digoxin dose by 30-50%. Appropriate monitoring of serum digoxin levels is recommended. Monitor P-gp substrate concentration for drugs with narrow therapeutic index.
ANTICOAGULANTS		
warfarin	↓ warfarin	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalized ratio (INR) is recommended.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole ↑ paritaprevir	Caution is warranted, and patients should be monitored for adverse reactions to ketoconazole and TECHNIVIE. The maximum daily dose of ketoconazole should not exceed 200 mg.
itraconazole and posaconazole	Not studied; theoretical ↑ itraconazole ↑ posaconazole ↑ paritaprevir	Drug interactions similar to ketoconazole are expected; monitor patients for adverse reactions and reduce the dose of the co-administered drug as appropriate.
voriconazole	Not studied; theoretical ↓ voriconazole ↑ paritaprevir	Co-administration of TECHNIVIE with voriconazole is recommended only if the assessment of the benefit-to-risk ratio justifies the use of voriconazole.

Concomitant Drug Class: Drug Name	Effect on Concentration of TECHNIVIE and/or Concomitant Drug	Clinical comments
ANTI-GOUT		
colchicine		Contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions (see **CONTRAINDICATIONS**). 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 Product Monograph).
CALCIUM CHANNEL BLOCKERS		
amlodipine[1]	↑ amlodipine	Caution is warranted and a 50% reduction in the dose of amlodipine should be considered.
diltiazem, nifedipine and verapamil	↑ diltiazem ↑ nifedipine ↑ verapamil	Decrease the dose of the calcium channel blocker. Clinical monitoring of patients is recommended.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone		Concomitant use of TECHNIVIE with inhaled or nasal fluticasone may decrease serum cortisol concentrations. Cases of Cushing's syndrome and adrenal suppression have been reported with ritonavir-containing regimens. Alternative corticosteroids should be considered, particularly for long term use.
DIURETICS		
furosemide[1]	↑ furosemide	Caution and monitoring for furosemide clinical effects are recommended; decrease the dose of furosemide by up to 50% if clinically indicated.
HIV-ANTIVIRAL AGENTS		
atazanavir	atazanavir administered in the morning ↔ atazanavir ↑ paritaprevir	Atazanavir should be taken without ritonavir with TECHNIVIE since ritonavir is included in TECHNIVIE. Atazanavir plus ritonavir is not recommended with TECHNIVIE.
darunavir	↓ darunavir (C_{trough})	Darunavir dose should be taken without ritonavir when co-administered with TECHNIVIE. Because of decreased darunavir trough concentrations, patients should be monitored for HIV-1viral breakthrough.

Concomitant Drug Class: Drug Name	Effect on Concentration of TECHNIVIE and/or Concomitant Drug	Clinical comments
HMG CoA REDUCTASE INHIBITORS		
fluvastatin	↑ fluvastatin	The lowest dose of fluvastatin should be used. Monitor patients for fluvastatin side effects such as myopathy/rhabdomyolysis.
rosuvastatin	↑ rosuvastatin	Rosuvastatin dose should not exceed 10 mg per day. Patients should be monitored for rosuvastatin side effects such as myopathy/rhabdomyolysis.
pravastatin	↑ pravastatin	Pravastatin dose should not exceed 40 mg per day. Patients should be monitored for pravastatin side effects such as myopathy/rhabdomyolysis.
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine ↑ paritaprevir	When starting co-administration with TECHNIVIE, give one fifth of the total daily dose of cyclosporine once daily. Monitor cyclosporine levels and adjust dose and/or dosing frequency as needed.
MUSCLE RELAXANTS		
carisoprodol[1]	↓ carisoprodol ↔ mepobramate (metabolite of carisoprodol)	Monitor patients for decreased efficacy of carisoprodol; increase the carisoprodol dose if clinically indicated.
cyclobenzaprine[1]	↓ cyclobenzaprine ↓ norcyclobenzaprine (metabolite of cyclobenzaprine)	Monitor patients for decreased efficacy of cyclobenzaprine; increase the cyclobenzaprine dose if clinically indicated.
NARCOTIC ANALGESICS		
buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine (metabolite of buprenorphine)	No dose adjustment of buprenorphine/naloxone is required.
hydrocodone[1] (when co-administered as a fixed-dose combination of 300 mg acetaminophen/5 mg hydrocodone)	↑ hydrocodone	Hydrocodone dose should be reduced by 50%. Monitor patients for respiratory depression and sedation at frequent intervals.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Monitor patients for decreased efficacy of omeprazole. Increase the omeprazole dose if clinically indicated.

Concomitant Drug Class: Drug Name	Effect on Concentration of TECHNIVIE and/or Concomitant Drug	Clinical comments
SEDATIVES/HYPNOTICS		
alprazolam[1]	↑ alprazolam	Caution is warranted and clinical monitoring of patients for alprazolam-associated side effects is recommended. A decrease in alprazolam dose can be considered based on clinical response.
diazepam[1]	↓ diazepam ↓ nordiazepam (metabolite of diazepam)	Monitor patients for decreased efficacy of diazepam; increase the diazepam dose if clinically indicated.

1. Drug interaction evaluated with ombitasvir and paritaprevir/ritonavir in combination with dasabuvir.

The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC)

Drugs with No Observed Interactions with TECHNIVIE

Drug interaction studies in patients reveal no clinically significant interaction between TECHNIVIE and the following commonly co-prescribed medications. No dose adjustments are required when co-administering these drugs with TECHNIVIE: abacavir, acetaminophen, dolutegravir, duloxetine, emtricitabine, escitalopram, gemfibrozil, lamivudine, metformin, methadone, naloxone, norethindrone, progestin only contraceptives, raltegravir, sofosbuvir, sulfamethoxazole, tenofovir disoproxil fumarate, trimethoprim, zolpidem.

Note: abacavir, acetaminophen, dolutegravir, lamivudine, metformin, progestin only contraceptives, sofosbuvir, sulfamethoxazole, thrimethoprim and zolpidem were evaluated with ombitasvir and paritaprevir/ritonavir in combination with dasabuvir.

Pharmacokinetic Parameters for Clinically Relevant Drug Interactions

Change in pharmacokinetic parameters for drug interactions resulting in contraindications, dose modification or clinical monitoring is presented in **Table 8** and **Table 9**. **Table 8** provides the magnitude of interaction on the individual components of TECHNIVIE and **Table 9** shows the effect on the concomitant medication. For information regarding clinical recommendations, see **Table 7**.

Table 8. Drug Interactions: Change in Pharmacokinetic Parameters of the Individual Components of TECHNIVIE in the Presence of Co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
ANTIARRHYTHMICS						
digoxin	0.5 single dose	11	ombitasvir	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)
			ritonavir	1.06 (0.99-1.13)	1.01 (0.98-1.05)	0.95 (0.86-1.04)
ANTICONVULSANTS						
carbamazepine[a]	200 once daily followed by 200 twice daily	12	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
			ritonavir	0.17 (0.12, 0.24)	0.13 (0.09, 0.17)	NA
ANTIFUNGALS						
ketoconazole	400 once daily	12	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
			ritonavir	1.27 (1.11, 1.45)	1.51 (1.36, 1.68)	NA
CALCIUM CHANNEL BLOCKERS						
amlodipine[a]	5 single dose	14	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)
			ritonavir	0.96 (0.87, 1.06)	0.93 (0.89, 0.98)	0.95 (0.89, 1.01)
DIURETICS						
furosemide[a]	20 single dose	12	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)
			ritonavir	1.10 (0.96, 1.27)	1.04 (0.92, 1.18)	1.07 (0.99, 1.17)
HIV-ANTIVIRAL AGENTS						
atazanavir[b]	300 once daily	10	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)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ritonavir	0.85 (0.72, 0.99)	0.97 (0.84, 1.13)	1.45 (1.29, 1.64)
darunavir[b]	800 once daily	9	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)
			ritonavir	0.83 (0.68, 1.01)	0.80 (0.73, 0.87)	0.91 (0.78, 1.06)
lopinavir/ ritonavir	400/100 twice daily	18	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)
			ritonavir	1.74 (1.39, 2.17)	2.78 (2.42, 3.20)	10.02 (7.66, 13.11)
lopinavir/ ritonavir[c]	800/200 once daily	11	ombitasvir	0.97 (0.87, 1.08)	1.09 (1.00, 1.19)	1.24 (1.13, 1.35)
			paritaprevir	1.78 (1.26, 2.52)	3.55 (2.37, 5.32)	14.78 (9.41, 23.23)
			ritonavir	1.80 (1.30, 2.48)	3.09 (2.36, 4.06)	23.16 (15.55, 34.51)
rilpivirine[a]	25 once daily (morning)[d]	10	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)
			ritonavir	1.10 (0.98, 1.24)	1.08 (0.93, 1.27)	0.97 (0.91, 1.04)
HMG CoA REDUCTASE INHIBITORS						
pravastatin	10 once daily	10	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)
			ritonavir	1.37 (1.05, 1.79)	1.37 (0.84, 2.24)	0.85 (0.76, 0.96)
rosuvastatin	5 mg once daily	12	ombitasvir	0.88 (0.81, 0.97)	0.88 (0.83, 0.92)	0.87 (0.83, 0.91)
			paritaprevir	1.40 (1.12, 1.74)	1.22 (1.10, 1.41)	1.10 (0.85, 1.32)
			ritonavir	1.10 (0.91, 1.22)	0.94 (0.84, 1.05)	0.77 (0.59, 1.00)
HORMONAL PRODUCT						
ethinyl estradiol/ norgestimate	Ethinyl estradiol 0.035 and	7[e]	ombitasvir	1.05 (0.81, 1.35)	0.97 (0.81, 1.15)	0.96 (0.88, 1.12)
			paritaprevir	0.70	0.66	0.87

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
	Norgestimate 0.25 once daily			(0.40, 1.21)	(0.42, 1.04)	(0.67, 1.14)
			ritonavir	0.80 (0.53, 1.21)	0.71 (0.54, 0.94)	0.79 (0.68, 0.93)
IMMUNOSUPPRESSANTS						
cyclosporine	10 single dose[f]	12	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)
			ritonavir	1.13 (0.94, 1.35)	1.20 (1.10, 1.30)	1.11 (0.89, 1.37)
tacrolimus	0.5 single dose[g]	11	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)
			ritonavir	0.88 (0.76, 0.93)	0.89 (0.85, 0.93)	1.04 (0.96, 1.13)
MUSCLE RELAXANTS						
carisoprodol[a]	250 single dose	14	ombitasvir	0.98 (0.92, 1.04)	0.95 (0.92, 0.97)	0.96 (0.92, 0.99)
			paritaprevir	0.88 (0.75, 1.03)	0.96 (0.85, 1.08)	1.14 (1.02, 1.27)
			ritonavir	0.94 (0.87, 1.02)	0.94 (0.88, 0.99)	0.95 (0.89, 1.03)
cyclobenzaprine[a]	5 single dose	14	ombitasvir	0.98 (0.92, 1.04)	1.00 (0.97, 1.03)	1.01 (0.98, 1.04)
			paritaprevir	1.14 (0.99, 1.32)	1.13 (1.00, 1.28)	1.13 (1.01, 1.25)
			ritonavir	0.93 (0.87, 0.99)	1.00 (0.95, 1.06)	1.13 (1.05, 1.21)
NARCOTIC ANALGESICS						
hydrocodone/acetaminophen[a]	5/300 single dose	15	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)
			ritonavir	1.01 (0.90, 1.13)	1.03 (0.96, 1.09)	1.01 (0.93, 1.10)
PROTON PUMP INHIBITORS						
omeprazole	40 once daily	12	ombitasvir	0.96 (0.81, 1.14)	1.00 (0.88, 1.12)	0.97 (0.89, 1.107)
			paritaprevir	1.02 (0.64, 1.62)	0.93 (0.64, 1.34)	0.83 (0.67, 1.04)
			ritonavir	1.06 (0.95, 1.18)	1.07 (0.96, 1.21)	1.07 (0.97, 1.18)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
SEDATIVES/HYPNOTICS						
alprazolam[a]	0.5 single dose	12	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)
			ritonavir	0.92 (0.84, 1.02)	0.96 (0.89, 1.03)	1.01 (0.94, 1.09)
diazepam[a]	2 single dose	13	ombitasvir	1.00 (0.93, 1.08)	0.98 (0.93, 1.03)	0.93 (0.88, 0.98)
			paritaprevir	0.95 (0.77, 1.18)	0.91 (0.78, 1.07)	0.92 (0.82, 1.03)
			ritonavir	1.10 (1.02, 1.19)	1.06 (0.98, 1.14)	0.98 (0.92, 1.03)

a. Study evaluated interaction with ombitasvir/paritaprevir/ritonavir plus dasabuvir; results extrapolated to ombitasvir/paritaprevir/ritonavir.
b. Atazanavir or darunavir administered with ombitasvir/paritaprevir/ritonavir in the morning was compared to atazanavir or darunavir administered with 100 mg ritonavir in the morning.
c. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of ombitasvir/paritaprevir/ritonavir.
d. Similar changes were observed when rilpivirine was dosed in the evening with food or 4 hours after food.
e. Data shown is combined data for ombitasvir/paritaprevir/ritonavir with (N=3) and without (N=4) dasabuvir.
f. 10 mg cyclosporine was administered with ombitasvir/paritaprevir/ritonavir in the test arm and 100 mg cyclosporine was administered in the reference arm without ombitasvir/paritaprevir/ritonavir.
g. 0.5 mg tacrolimus was administered with ombitasvir/paritaprevir/ritonavir in the test arm and 2 mg tacrolimus was administered in the reference arm without ombitasvir/paritaprevir/ritonavir.

NA: not available/not applicable; DAA: Direct-acting antiviral agent; CI: Confidence interval
Doses of ombitasvir, paritaprevir, ritonavir were 25 mg, 150 mg and 100 mg, respectively.
For studies conducted with ombitasvir/paritaprevir/ritonavir plus dasabuvir, doses of dasabuvir were 250 mg or 400 mg (both doses showed similar exposures).
Ombitasvir, paritaprevir and ritonavir were dosed once daily (and where applicable, dasabuvir was dosed twice daily) in all the above studies except studies with ketoconazole and carbamazepine that used single doses.

Table 9 summarizes the effects of TECHNIVIE on the pharmacokinetics of co-administered drugs which showed clinically relevant changes. For information regarding clinical recommendations, see **Table 7**.

Table 9. Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of TECHNIVIE

Co-administered Drug	Dose of Co-administered Drug (mg)	n	Ratio (with/without TECHNIVIE) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			C_{max}	AUC	C_{min}
ANTIARRHYTHMICS					
digoxin	0.5 single dose	11	1.58 (1.43-1.73)	1.36 (1.21-1.53)	1.24 (1.07-1.43)[k]
ANTICOAGULANTS					
s-warfarin	5 mg single dose	11	0.90 (0.82, 0.99)	0.85 (0.76, 0.95)	0.89 (0.84, 0.93)
r-warfarin			0.96 (0.88, 1.05)	0.87 (0.82, 0.91)	0.87 (0.84, 0.91)
ANTICONVULSANTS					
carbamazepine[a]	200 once daily followed by 200 twice daily	12	1.10 (1.07, 1.14)	1.17 (1.13, 1.22)	1.35 (1.27, 1.45)
carbamazepine's metabolite, carbamazepine-10,11-epoxide (CBZE)			0.84 (0.82, 0.87)	0.75 (0.73, 0.77)	0.57 (0.54, 0.61)
ANTIFUNGALS					
ketoconazole	400 once daily	12	1.10 (1.05, 1.16)	2.05 (1.93, 2.18)	NA
CALCIUM CHANNEL BLOCKERS					
amlodipine[a]	5 single dose	14	1.26 (1.11, 1.44)	2.57 (2.31, 2.86)	NA
DIURETICS					
furosemide[a]	20 single dose	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	NA
HIV-ANTIVIRAL AGENTS					
atazanavir[b]	300 once daily	11	0.90 (0.83, 0.97)	0.93 (0.85, 1.02)	0.81 (0.72, 0.91)
darunavir[b]	800 once daily	9	0.99 (0.92, 1.08)	0.92 (0.84, 1.00)	0.74 (0.63, 0.88)
lopinavir/ritonavir[c]	400/100 twice daily	18	1.06 (0.99, 1.14)	1.13 (1.09, 1.17)	1.34 (1.26, 1.42)
lopinavir/ritonavir[c,d]	800/200 once daily	12	1.05 (0.95, 1.17)	1.17 (1.09, 1.26)	3.50 (2.69, 4.56)
rilpivirine[a]	25 once daily (morning)[e]	8	2.55 (2.08, 3.12)	3.25 (2.80, 3.77)	3.62 (3.12, 4.21)
HMG CoA REDUCTASE INHIBITORS					
pravastatin	10 once daily	10	1.43 (1.09, 1.88)	1.76 (1.46, 2.13)	NA
rosuvastatin	5 mg once daily	12	2.61 (2.01, 3.39)	1.33 (1.14-1.56)	0.65 (0.57-0.74)
HORMONAL PRODUCT					
ethinyl Estradiol[f]	Ethinyl estradiol 0.035 and Norgestimate 0.25	8	1.16 (0.90, 1.50)	1.06 (0.96, 1.17)	1.12 (0.94, 1.33)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	Ratio (with/without TECHNIVIE) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			C_{max}	AUC	C_{min}
norelgestromin[f]	once daily	9	2.01 (1.77, 2.29)	2.60 (2.30, 2.95)	3.11 (2.51, 3.85)
norgestref		9	2.26 (1.91, 2.67)	2.54 (2.09, 3.09)	2.93 (2.39, 3.57)
IMMUNOSUPPRESSANTS					
cyclosporine	10 single dose[g]	12	0.83 (0.72, 0.94)[h]	4.28 (3.66, 5.01)[h]	12.85 (10.61, 15.55)[h,k]
everolimus	0.75 single dose	12	4.74 (4.29, 5.25)	27.12 (24.5, 30.1)	16.10 (14.5, 17.9)[a,j]
sirolimus	0.5 single dose[k]	11	6.40 (5.34, 7.68)[h]	37.99 (31.5, 45.8)[h]	19.55 (16.7, 22.9)[a,h,k]
tacrolimus	0.5 single dose[i]	11	4.27 (3.49, 5.22)[h]	85.81 (67.88, 108.49)[h]	24.61 (19.69, 30.77)[h,k]
MUSCLE RELAXANTS					
carisoprodol[a]	250 single dose	14	0.54 (0.47, 0.63)	0.62 (0.55, 0.70)	NA
carisoprodol's metabolite, mepobramate			1.17 (1.10, 1.25)	1.09 (1.03, 1.16)	NA
cyclobenzaprine[a]	5 single dose	14	0.68 (0.61, 0.75)	0.60 (0.53, 0.68)	NA
cyclobenzaprine's metabolite norcyclobenzaprine			1.03 (0.87, 1.23)	0.74 (0.64, 0.85)	NA
NARCOTIC ANALGESICS					
hydrocodone[a]	5 single dose	15	1.27 (1.14, 1.40)	1.90 (1.72, 2.10)	NA
PROTON PUMP INHIBITORS					
omeprazole	40 once daily	12	0.48 (0.29, 0.78)	0.46 (0.27, 0.77)	NA
SEDATIVES/HYPNOTICS					
alprazolam[a]	0.5 single dose	12	1.09 (1.03, 1.15)	1.34 (1.15, 1.55)	NA
diazepam[a]	2 single dose	13	1.18 (1.07, 1.30)	0.78 (0.73, 0.82)	NA
diazepam's metabolite nordiazepam			1.10 (1.03, 1.19)	0.56 (0.45, 0.70)	NA

a. Study evaluated interaction with ombitasvir/paritaprevir/ritonavir plus dasabuvir; results extrapolated to ombitasvir/paritaprevir/ritonavir.
b. Atazanavir or darunavir administered with ombitasvir/paritaprevir/ritonavir in the morning
c. Lopinavir parameters are reported.
d. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of ombitasvir/paritaprevir/ritonavir.
e. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.
f. Data shown are combined data for ombitasvir/paritaprevir/ritonavir with (N=3) and without (N=6, except for EE where N=5) dasabuvir.
g. 10 mg cyclosporine was administered with ombitasvir/paritaprevir/ritonavir in the test arm and 100 mg

Co-administered Drug	Dose of Co-administered Drug (mg)	n	Ratio (with/without TECHNIVIE) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			C_{max}	AUC	C_{min}

cyclosporine was administered in the reference arm without ombitasvir/paritaprevir/ritonavir.

h. Dose normalized parameters reported.

i. 0.5 mg tacrolimus was administered with ombitasvir/paritaprevir/ritonavir in the test arm and 2 mg tacrolimus was administered in the reference arm without ombitasvir/paritaprevir/ritonavir.

j. C_{12}: concentration at 12 hours following single dose of everolimus.

k. C_{24}: concentration at 24 hours following single dose of cyclosporine, tacrolimus or sirolimus.

l. 0.5 mg sirolimus was administered with ombitasvir/paritaprevir/ritonavir plus dasabuvir in the test arm and 2 mg sirolimus was administered in the reference arm without ombitasvir/paritaprevir/ritonavir plus dasabuvir.

NA: not available/not applicable; CI: Confidence interval.
Doses of ombitasvir, paritaprevir and ritonavir were 25 mg, 150 mg and 100 mg, respectively.
For studies conducted with ombitasvir/paritaprevir/ritonavir plus dasabuvir, doses of dasabuvir were 250 mg or 400 mg (both doses showed similar exposures).
Ombitasvir, paritaprevir and ritonavir were dosed once daily (and where applicable, dasabuvir was dosed twice daily) in all the above studies except studies with ketoconazole and carbamazepine that used single doses.

Drug-Food Interactions

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 maximize absorption, TECHNIVIE should be taken with food without regard to fat or calorie content (see **DOSAGE AND ADMINISTRATION**).

Drug-Herb Interactions

Co-administration of St. John's Wort *(Hypericum perforatum)*, a potent hepatic and intestinal CYP3A4 and/or P-gp inducer, may decrease TECHNIVIE plasma concentrations, which may result in loss of therapeutic effect.

St. John's Wort *(Hypericum perforatum)* is contraindicated with TECHNIVIE (see **CONTRAINDICATIONS**).

Drug-Laboratory Interactions

Interactions of TECHNIVIE with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- TECHNIVIE is a fixed dose combination (FDC) tablet of ombitasvir/paritaprevir/ritonavir.

- TECHNIVIE is used in combination with ribavirin in patients with genotype 4 chronic hepatitis C infection.

- Prior to initiation of therapy, assess for laboratory and clinical evidence of hepatic decompensation (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).

- TECHNIVIE tablets should be swallowed whole, with water if required, and not chewed, broken, or crushed.

Recommended Dose and Dosage Adjustment

The recommended oral dose of TECHNIVIE is two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets taken once daily (in the morning) with food without regard to fat or calorie content (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Absorption**, *Effects of Food on Oral Absorption*).

As a fixed dose combination formulation, no dosage adjustments for TECHNIVIE are possible.

TECHNIVIE tablets should be used in combination with ribavirin (RBV).

For specific dosage instructions for ribavirin and dose modifications, refer to the prescribing information of ribavirin.

The recommended treatment regimen and duration based on patient population is provided in **Table 10**.

Table 10. Recommended Treatment Regimen and Treatment Duration for HCV Genotype-4 Treatment-naïve[a] and Treatment-experienced[b] Patients without Cirrhosis or with Compensated Cirrhosis

Patient Population	Treatment	Duration
Genotype 4	TECHNIVIE[c] + RBV[d,e] (ombitasvir/paritaprevir/ritonavir + RBV) Two Tablets, QD	12 weeks

a. Treatment naïve was defined as not having received any prior therapy for HCV infection.
b. Treatment-experienced patients were defined as either: prior relapsers (received at least 36 weeks of pegIFN/RBV treatment and HCV RNA was undetectable at the end of 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 10 weeks of pegIFN/RBV treatment and failed to achieve a 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12).
c. The recommended regimen is the co-formulated combination of ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg), two tablets once daily (see **Recommended Dose and Dosage Adjustment** of **DOSAGE AND ADMINISTRATION**). The clinical trial was conducted with the individual components (see **CLINICAL TRIALS**).
d. RBV, ribavirin. When administered with TECHNIVIE, the recommended dosage of RBV is based on weight: 1000 mg for patients <75 kg and 1200 mg/day for those ≥75 kg, divided and administered twice-daily with food.
e. 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 or dose modification. If TECHNIVIE used in combination with ribavirin, ribavirin should be administered for the same duration as TECHNIVIE.

Special Populations

Pediatrics (< 18 years of age)

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

Geriatrics (≥ 65 years of age)

No dose adjustment of TECHNIVIE is warranted in geriatric patients (see **INDICATIONS AND CLINICAL USE**; **WARNINGS AND PRECAUTIONS**, **Geriatrics**; **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Hepatic Impairment

No dose adjustment of TECHNIVIE is required in patients with mild hepatic impairment (Child-Pugh A). TECHNIVIE is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) (see **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**; **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

Renal Impairment

No dose adjustment of TECHNIVIE is required in patients with mild, moderate or severe renal impairment (see **WARNINGS AND PRECAUTIONS, Renal Impairment** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

TECHNIVIE has not been studied in patients on dialysis.

Missed Dose

Patients should be informed that in case a dose of ombitasvir/paritaprevir/ritonavir is missed, the prescribed dose can be taken within 12 hours of the scheduled time for the dose that was missed.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The highest documented single dose administered to healthy subjects was 350 mg for ombitasvir, 400 mg for paritaprevir (with 100 mg ritonavir) and 200 mg for ritonavir (with 100 mg paritaprevir). 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 and appropriate symptomatic treatment instituted immediately. ECG monitoring is recommended.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TECHNIVIE (ombitasvir/paritaprevir/ritonavir) 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 (see **MICROBIOLOGY**, **Mechanism of Action**).

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. Ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication. The stopping of viral replication leads to a rapid decline of HCV viral load and clearing of HCV levels in the body.

Ritonavir is not active against HCV. Ritonavir is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (i.e., area under the curve).

Pharmacodynamics

Effects on Electrocardiogram

The effect of a combination of paritaprevir, ombitasvir, ritonavir, and dasabuvir on QTc interval was evaluated in a randomized, double blind, placebo and active-controlled (moxifloxacin 400 mg) 4-way crossover thorough QT study in 60 healthy subjects. At concentrations approximately 6 and 1.8 times the therapeutic concentrations of paritaprevir and ombitasvir, the combination did not prolong QTc to any clinically relevant extent.

Pharmacokinetics

The pharmacokinetic properties of the combination of ombitasvir, paritaprevir and ritonavir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C infection. **Table 11** shows mean C_{max} and AUC of ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily following multiple doses with food in healthy subjects (**Table 11**).

Table 11. Geometric Mean Steady-State Exposures of Ombitasvir/Paritaprevir/Ritonavir 25/150/100 mg Once Daily with Food in HCV GT4 Non-Cirrhotic Patients and Healthy Subjects

Compound/Population	AUC (ng·h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
HCV-Infected Patients*			
Ombitasvir	1210	78.1	20.5
Paritaprevir	2320	198	12.4
Ritonavir	5620	478	35.7
Healthy Subjects			
Ombitasvir	1370	120	29
Paritaprevir	4770	807	18
Ritonavir	8090	1330	32

* Pharmacokinetic parameters in HCV-infected patients derived from population pharmacokinetic analysis of sparse samples collected from GT-4 infected patients in Study M13-393.

Paritaprevir C_{max} and AUC from the ombitasvir/paritaprevir/ritonavir co-formulated tablet are 93% and 63% higher, respectively, compared to exposures of paritaprevir formulation administered in combination with ritonavir and ombitasvir formulations in PEARL-I.

Absorption

In clinical trials in healthy subjects, ombitasvir/paritaprevir/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 is achieved after approximately 12 days of dosing.

The absolute bioavailability of ombitasvir and paritaprevir when administered with ritonavir as TECHNIVIE is approximately 48.1 and 52.6%, respectively.

Effects of Food on Oral Absorption

A moderate fat meal (approximately 600 Kcal, 20-30% calories from fat) increased the exposure (AUC) of ombitasvir, paritaprevir and ritonavir by up to 82, 211 and 49%, respectively relative to the fasting state.

A high fat meal (approximately 900 Kcal, 60% calories from fat) increased the mean AUC of ombitasvir, paritaprevir and ritonavir with by 76, 180, and 44%, respectively relative to 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).

Distribution

Ombitasvir, paritaprevir and ritonavir are highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood to plasma concentration ratios in humans ranged from 0.6 to 0.8, indicating that ombitasvir and paritaprevir were preferentially distributed in the plasma compartment of whole blood.

Ombitasvir

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

In animals, paritaprevir liver levels are significantly higher than plasma levels (e.g. liver: plasma ratio of greater than 300:1 in mouse). *In vitro* data indicate that paritaprevir is a substrate for the human hepatic uptake transporters, OATP1B1 and OATP1B3.

Paritaprevir

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

Ritonavir

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

Metabolism

Ombitasvir

Ombitasvir is metabolized 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 metabolized predominantly by CYP3A4 and to a lesser extent CYP3A5. Following administration of a single 200/100 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 metabolized 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.

Excretion

Ombitasvir

Following a 25 mg ^{14}C-ombitasvir dose, approximately 90.2% of the radioactivity was recovered in feces with limited radioactivity (1.91%) in urine; unchanged ombitasvir accounted for 87.8% of the radioactivity in the feces and 0.03% in the urine. The mean elimination half-life of ombitasvir was approximately 21 to 25 hours.

Paritaprevir

Following a 200 mg ^{14}C-paritaprevir dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in feces with limited radioactivity (8.8%) in urine; unchanged paritaprevir accounted for 1.1% of the radioactivity in the feces and 0.05% in the urine. Unchanged parent drug and M29, the product of fecal hydrolysis, accounted for 87.8% of total radioactivity recovered in feces, indicating that biliary excretion of parent drug is a major elimination pathway for paritaprevir. The mean plasma half-life of paritaprevir was approximately 5.5 hours.

Ritonavir

Following dosing of paritaprevir/ritonavir/ombitasvir, 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 feces and 11.3% of the dose was excreted in the urine.

Ombitasvir, paritaprevir and ritonavir do not inhibit organic anion transporter (OAT1) in vivo and, based on in vitro data, are not expected to inhibit organic cation transporter (OCT2), organic anion transporter (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations.

Ombitasvir, paritaprevir and ritonavir are neither inhibitors nor substrates of organic cation transporter 1 (OCT1).

Special Populations and Conditions

Pediatrics

The pharmacokinetics of TECHNIVIE in pediatric patients has not been established (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pediatrics (< 18 years of age)**).

Geriatrics (> 65 years of age)

Due to the limited number of patients at least 65 years of age in the clinical trial PEARL-I, the effect of age on pharmacokinetics could not be determined. Population pharmacokinetic analysis of data from Phase 3 clinical trials with ombitasvir, paritaprevir and ritonavir with dasabuvir showed that a 10 year increase or decrease in age from 54 years (median age in the Phase 3 trials) would result in approximately 10% change in ombitasvir exposures and ≤ 20% change in paritaprevir exposures. Age was not a significant predictor for ritonavir exposures. There is no pharmacokinetic information in patients at least 75 years of age. Phase 3 studies of ombitasvir, paritaprevir and ritonavir with dasabuvir included 174 patients at least 65 years of age (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics (> 65 years of age)**.

Gender

Based on population pharmacokinetic analyses in HCV genotype 4-infected patients in the clinical trial PEARL-I, sex had no effect on paritaprevir or ritonavir exposures; male patients would have approximately 29 to 37% lower ombitasvir exposures (C_{max}, AUC_{ss} and C_{min}) than female patients. These effects do not warrant dose adjustments of ombitasvir based on sex.

Race

Based on PEARL-I population pharmacokinetic analyses, exposures of ombitasvir, paritaprevir, and ritonavir were not significantly different in HCV genotype 4-infected patients of Black race compared to patients of other races. Due to the limited number of patients enrolled in PEARL-I, the effect of other ethnicities on pharmacokinetics could not be determined. Ethnicities have been evaluated in Phase 3 studies of ombitasvir, paritaprevir and ritonavir in combination with

dasabuvir. Population pharmacokinetic analysis of data from Phase 3 clinical trials with ombitasvir, paritaprevir and ritonavir with dasabuvir showed that Asian patients had 18 to 21% higher ombitasvir exposures, and 37 to 39% higher paritaprevir exposures than non-Asian patients. The ritonavir exposures were comparable between Asians and non-Asians. These differences in exposures were not clinically significant.

Hepatic Insufficiency

Pharmacokinetics of ombitasvir, paritaprevir and ritonavir were not evaluated in patients with hepatic impairment.

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

In patients with mild hepatic impairment ombitasvir, paritaprevir, and ritonavir mean AUC values decreased by 8, 29 and 34%, respectively compared to patients with normal hepatic function. No dose adjustment for TECHNIVIE is recommended for HCV-infected patients with mild hepatic impairment.

In patients with moderate hepatic impairment, ombitasvir and ritonavir mean AUC values decreased by 30%, paritaprevir mean AUC value increased by 62%, compared to patients with normal hepatic function. TECHNIVIE is contraindicated in patients with moderate hepatic impairment (Child-Pugh B).

In patients with severe hepatic impairment, paritaprevir mean AUC values increased by 945%, ritonavir mean AUC value was 13% higher and ombitasvir mean AUC value decreased by 54% compared to patients with normal hepatic function.

TECHNIVIE is contraindicated in patients with severe hepatic impairment (Child-Pugh C).

Renal Insufficiency

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 150 mg and ritonavir 100 mg, were evaluated in non-HCV infected patients with mild (creatinine clearance [CrCl]: 60 to 89 mL per min), moderate (CrCl: 30 to 59 mL per min) and severe (CrCl: 15 to 29 mL per min) renal impairment.

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

In patients with mild renal impairment, the mean ritonavir AUC values increased by 40%, while ombitasvir and paritaprevir AUC values were unchanged compared to patients with normal renal function.

In patients with moderate renal impairment, the mean ritonavir AUC values increased by 76%, while ombitasvir and paritaprevir AUC values were unchanged compared to patients with normal renal function.

In patients with severe renal impairment, the mean paritaprevir and ritonavir AUC values increased by 25 and 108%, respectively, while ombitasvir AUC values were unchanged compared to patients with normal renal function.

Consult the Product Monograph of ribavirin in renal impairment patients.

STORAGE AND STABILITY

Store between 2 and 30°C. Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TECHNIVIE is a pink-colored, film-coated, oblong, biconvex-shaped tablet debossed “AV1” on one side. Each tablet contains 12.5 mg ombitasvir, 75 mg paritaprevir and 50 mg ritonavir.

TECHNIVIE is dispensed in a convenient 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 12.5/75/50 mg ombitasvir/paritaprevir/ritonavir tablets.

Listing of Non-Medicinal Ingredients

Each ombitasvir/paritaprevir/ritonavir fixed dose combination tablet contains 12.5 mg ombitasvir /75 mg paritaprevir/50 mg ritonavir with the following non-medicinal ingredients: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, propylene glycol monolaurate, sodium stearyl fumarate, sorbitan monolaurate, and vitamin E polyethylene glycol succinate. The film-coating ingredients include: iron oxide red, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide. The tablets do not contain gluten.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

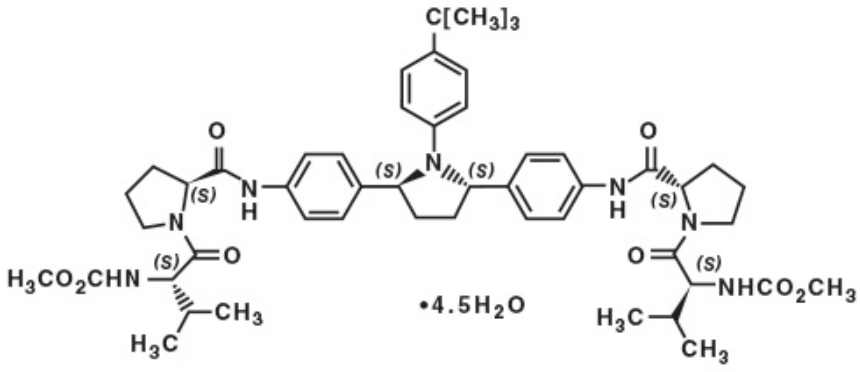
Ombitasvir Hydrate

Common name: ombitasvir

Chemical name: Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate

Molecular formula and molecular mass: $C_{50}H_{67}N_7O_8 \bullet 4.5H_2O$ (hydrate) 975.20 (hydrate)

Structural formula:

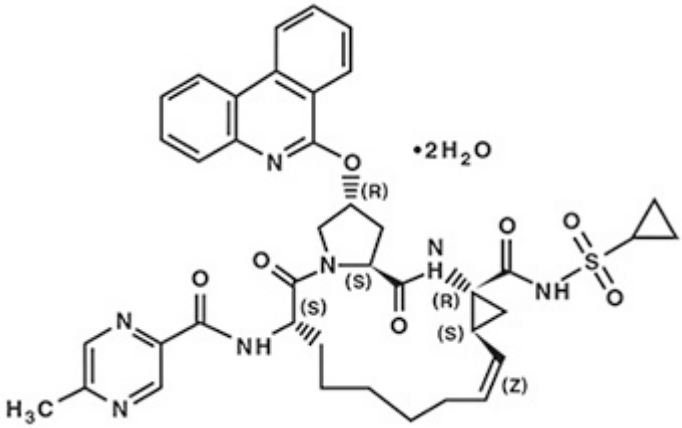


Physicochemical properties:

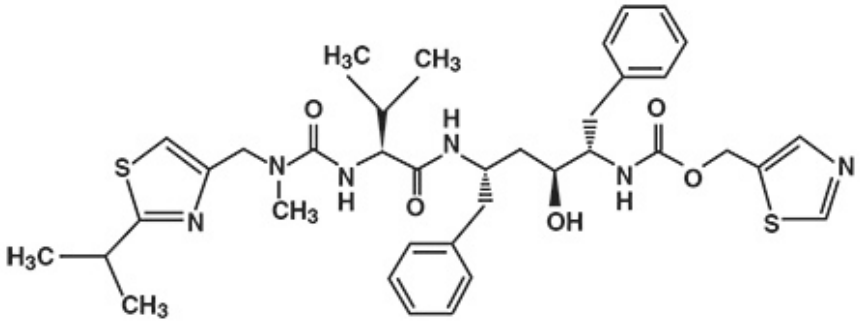
Appearance: Ombitasvir Hydrate is a white to light yellow to light pink powder.

Solubility: Ombitasvir Hydrate is practically insoluble in aqueous buffers but is soluble in ethanol.

Paritaprevir Hydrate

Common name:	paritaprevir
Chemical name:	(2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate
Molecular formula and molecular mass:	$C_{40}H_{43}N_7O_7S \bullet 2H_2O$ (dihydrate) 801.91 (dihydrate)
Structural formula:	
Physicochemical properties:	
Appearance	Paritaprevir Hydrate is a white to off-white powder.
Solubility	Paritaprevir Hydrate has very low water solubility.

Ritonavir

Proper name:	ritonavir
Chemical name:	[5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methyethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester
Molecular formula and molecular mass:	$C_{37}H_{48}N_6O_5S_2$ 720.95
Structural formula:	
Physicochemical properties:	
Appearance	Ritonavir is a white to off white to light tan powder.
Solubility	Ritonavir is insoluble in water and freely soluble in methanol and ethanol.

CLINICAL TRIALS

Trial Design

The efficacy and safety of ombitasvir, paritaprevir and ritonavir was evaluated in two clinical trials in patients with genotype 4 chronic hepatitis C infection (PEARL-I and AGATE-I), as summarized in **Table 12**.

Table 12. Summary of Clinical Trial Designs in Treatment of Genotype 4 Chronic Hepatitis C Infection

Study #	Trial Design	Regimen, Dosage and Number of Patients	Duration of treatment Weeks
PEARL-I (M13-393)	Open-label, randomized to administer with or without RBV	**(**paritaprevir tablet: 150 mg; ombitasvir tablet: 25 mg; ritonavir soft gelatin capsule: 100 mg**)** once daily (QD) + RBV[a]. N=135	12 weeks
AGATE-I (M11-665)	Open-label, administer with RBV	coformulated ombitasvir/paritaprevir/ritonavir 25/150/100 mg tablets QD + RBV[a] N=120	12 weeks or 16 weeks

a. RBV, ribavirin tablets. The ribavirin dose was 1,000 mg per day for patients weighing less than 75 Kg and 1,200 mg per day for patients weighing ≥ 75 Kg.

In both trials, TECHNIVIE was administered with food and weight based ribavirin. The ribavirin dosage was 1000 mg per day for patients weighing less than 75 kg or 1200 mg per day for patients weighing greater than or equal to 75 kg. The primary endpoint in both trials 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. Previous exposure to HCV direct-acting antivirals was prohibited.

PEARL-I

PEARL-I was a randomized, global multicenter, open-label trial that enrolled 135 adults without cirrhosis who were either treatment-naïve or did not achieve SVR with prior treatment with pegylated interferon/RBV (pegIFN/RBV). Treatment-naïve patients were randomized in a 1:1 ratio to receive ombitasvir tablets, paritaprevir tablets and ritonavir capsules with or without ribavirin for 12 weeks. PegIFN/RBV treatment-experienced patients received ombitasvir tablets, paritaprevir tablets and ritonavir capsules in combination with ribavirin for 12 weeks.

AGATE-I

AGATE-I was a global multicenter, open-label trial in adults with compensated cirrhosis who were either treatment-naïve or pegIFN/RBV treatment-experienced. TECHNIVIE was administered as coformulated ombitasvir, paritaprevir, ritonavir tablets in combination with ribavirin for 12 or 16 weeks.

Demographic and baseline characteristics for adult patients with genotype 4 chronic hepatitis C infection in PEARL-I and AGATE-I are provided in **Table 13.**

Table 13. Demographic and Baseline Characteristics of Treatment-Naïve and Treatment-Experienced HCV Genotype 4-Infected Patients in PEARL-I and AGATE-I

	PEARL-I	**AGATE-I**
Characteristics	**Ombitasvir + Paritaprevir + Ritonavir ± RBV 12 Weeks N = 135 n (%)**	**Ombitasvir + Paritaprevir + Ritonavir + RBV 12 or 16 Weeks N = 120 n (%)**
Age (years)		
Median (range)	51 (19 - 70)	56 (32 - 81)
Gender		
Male	88 (65.2)	84 (70.0)
Female	47 (34.8)	36 (30.0)
Race		
White	120 (88.9)	95 (79.2)
Black or African American	12 (8.9)	20 (16.7)
Asian	0	4 (3.3)
Other	2 (1.5)	(0.8)
Multi-race	1 (0.7)	0
Ethnicity		
Hispanic or Latino	8 (5.9)	3 (2.5)
None of the above	127 (94.1)	117 (97.5)
Body mass index		
< 30 kg/m^2	116 (85.9)	86 (71.7)
≥ 30 kg/m^2	19 (14.1)	34 (28.3)
HCV genotype*		
4a	50 (37.9)	64 (53.3)
4b	3 (2.3	0
4d	68 (51.5)	31 (25.8)
4f	7 (5.3)	3 (2.5)

	PEARL-I	AGATE-I
Characteristics	**Ombitasvir + Paritaprevir + Ritonavir ± RBV 12 Weeks N = 135 n (%)**	**Ombitasvir + Paritaprevir + Ritonavir + RBV 12 or 16 Weeks N = 120 n (%)**
4 other subtypes	3 (2.3) **	20 (16.7) ***
4 (subtype could not be determined)	1 (0.8)	2 (1.7)
Treatment History		
Treatment-naïve	86 (63.7)	60 (50.0)
Prior pegIFN/RBV null responder	23 (17.0)	33 (27.5)
Prior pegIFN/RBV partial responder	9 (6.7)	12 (10)
Prior pegIFN/RBV relapser	17 (12.6)	15 (12.5)
Baseline HCV RNA		
Mean ± SD (log_{10} IU/mL)	6.17 + 0.53	6.1 ± 0.66
< 800000 IU/mL, n (%)	41 (30.4)	32 (26.7)
≥ 800000 IU/mL, n (%)	94 (69.6)	88 (73.3)
IL28B		
CC	29 (21.5)	19 (15.8)
Non-CC	106 (78.5)	101 (84.2)
Baseline fibrosis stage[#]		
F0-F1	104 (77.0)	NA
F2	21 (15.6)	NA
F3	9 (6.7)	NA
F4	1 (0.7)	NA
Baseline platelet counts (x 10^9/L)		
<60	NA	5 (4.2)
60-<90	NA	15 (12.5)
90 - <120	NA	16 (13.3)
>=120	NA	84 (70.0)
Baseline albumin (g/L)		
< 35	NA	5 (4.2)
>= 35	NA	115 (95.8)
History of depression		
No	120 (88.9)	104 (86.7)

	PEARL-I	AGATE-I
Characteristics	**Ombitasvir + Paritaprevir + Ritonavir ± RBV 12 Weeks N = 135 n (%)**	**Ombitasvir + Paritaprevir + Ritonavir + RBV 12 or 16 Weeks N = 120 n (%)**
Yes	15 (11.1)	16 (13.3)

* HCV genotype 4 subtype determined by phylogenetic analysis.

**One (1) each of 4c, 4g/k, and 4o

*** One (1) each of 4e, 4h, 4o, 4q, 4r and 4t; Two (2) each of 4l, 4n and 4p; Four (4) each of 4c and 4k.

#Fibrosis score was obtained in PEARL-I; in AGATE-I all patients had compensated cirrhosis.

Study Results

The SVR12 rates for HCV genotype 4-infected patients who were treatment-naïve or previously treated with pegIFN/RBV are summarized in **Table 14**.

Table 14. Sustained Virologic Response (SVR12) for HCV Genotype 4-Infected Patients who were Treatment-Naïve or Treatment-Experienced Patients without Cirrhosis (PEARL-I) and with Compensated Cirrhosis (AGATE-I)

	PEARL-I			AGATE-I	
Treatment outcome	**Ombitasvir + Paritaprevir + Ritonavir[b] with RBV 12 weeks**		**Ombitasvir + Paritaprevir + Ritonavir[b] No RBV 12 weeks**	**Ombitasvir + Paritaprevir + Ritonavir with RBV 12 weeks**	**Ombitasvir + Paritaprevir + Ritonavir with RBV 16 weeks**
	Treatment-naïve % (n/N)	**Treatment-experienced[a] % (n/N)**	**Treatment-naïve % (n/N)**	**Treatment-naïve and Treatment-experienced[a] % (n/N)**	**Treatment-naïve and Treatment-experienced[a] % (n/N)**
Overall SVR12 **95% CI[c]**	100 (42/42) 91.6 to 100	100 (49/49) 92.7 to 100	91 (40/44) 78.3 to 97.5	97 (57/59) 88.5 to 99.1	98 (60/61) 91.3 to 99.7
Outcome for Patients without SVR12					
On-treatment VF[d]	0 (0/42)	0 (0/49)	2 (1/44)	2 (1/59)	0 (0/61)
Relapse[e]	0 (0/42)	0 (0/49)	5 (2/42)	0 (0/57)	0 (0/59)
Other[f]	0 (0/42)	0 (0/49)	2 (1/44)	2 (1/59)	2 (1/61)

a; Patients previously treated with PegIFN alfa plus ribavirin.
b; Ombitasvir tablets, Paritaprevir Tablets and Ritonavir capsules were administered separately.
c; Calculated using Clopper-Pearson exact method for PEARL-I and Wilson score method for AGATE-I.
d; VF, Virologic Failure. 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.
e; Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

f; Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. lost to follow-up).

Paritaprevir total exposures (AUC) are 63% higher from the co-formulated tablet compared to the exposures from the tablet formulation used in PEARL-I.

Among the 131 patients in PEARL-I who achieved SVR12, virologic response data at post-treatment week 24 were available from 129 patients, and 129/129 (100%) patients maintained their response through 24 weeks post-treatment (SVR24).

Impact of Baseline Factors

Baseline viral load (< 800,000 IU/ml and ≥ 800,000 IU/ml) and host factors including gender, race, ethnicity, age, IL28B allele, baseline body mass index, history of depression, fibrosis stage, were not associated with SVR12 rate differences based on a limited number of patients.

Impact of Ribavirin Dose Adjustment on Probability of SVR

In the PEARL-I clinical trial, all patients (100%) receiving ombitasvir, paritaprevir, and ritonavir with ribavirin achieved SVR, including 7.7% of patients who had ribavirin dose adjustments during therapy.

MICROBIOLOGY

Mechanism of Action

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

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A which is essential for viral RNA replication and virion assembly. The mechanism of action of ombitasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

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. In a biochemical assay, paritaprevir inhibited the proteolytic activity of a recombinant HCV genotype 4a NS3/4A protease enzyme with a half maximal inhibitory concentration (IC_{50}) value of 0.16 nM.

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.

Activity in Cell Culture and/or Biochemical Studies

Ombitasvir

The EC_{50} values of ombitasvir against HCV replicons containing NS5A from a single isolate of genotype 4a and 4d were 1.7 pM and 0.38 pM, respectively. 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.

Paritaprevir

The EC_{50} values of paritaprevir against HCV replicons containing NS3 from a single isolate of genotype 4a and 4d were 0.09 nM and 0.015 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.

Resistance in Cell Culture

Exposure of HCV genotype 4a replicons to paritaprevir or ombitasvir resulted in the emergence of drug resistant replicons carrying amino acid substitutions in NS3 or NS5A, respectively. Amino acid substitutions in NS5A or NS3 selected in cell culture or identified in the clinical trial PEARL-I were phenotypically characterized in genotype 4 replicons. For paritaprevir, in the HCV genotype 4a replicon, NS3 substitutions R155C, A156T/V, and D168H/V reduced paritaprevir antiviral activity by 40- to 323-fold. In the 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.

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

respectively. Ombitasvir retained full activity against the common NS5A polymorphisms M31I/L and T58A/P/S in NS5A in HCV genotype 4d.

Effect of Baseline HCV Substitutions/Polymorphisms on Treatment Response

Phylogenetic analysis of HCV sequences from genotype 4-infected patients in the clinical trial PEARL-I identified 7 HCV genotype 4 subtypes (4a, 4b, 4c, 4d, 4f, 4g/4k, 4o). Most patients were infected with either subtype 4a (38%) or 4d (52%); 1 to 7 patients were infected with each of the other genotype 4 subtypes. Three patients who experienced virologic failure with the regimen containing paritaprevir/ritonavir and ombitasvir without ribavirin were infected with HCV subtype 4d. Baseline sequence analysis (n=132) indicated that amino acids at positions 28, 30, 31 and 58 in NS5A were polymorphic. Baseline polymorphisms were not observed at signature resistance-associated positions in NS3.

Phylogenetic analysis of HCV sequences from gentotype 4-infected subjects in the clinical trial 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 trial 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 rates observed in PEARL-I and AGATE-I.

Resistance in Clinical Studies

In the clinical trial PEARL-I, three patients with HCV genotype 4 infection experienced virologic failure (2 post-treatment relapse, 1 on-treatment failure). All 3 virologic failures were observed with a regimen containing paritaprevir/ritonavir and ombitasvir without ribavirin and all 3 were infected with genotype 4d which was the predominant subtype isolated. None of these patients had resistance-conferring variants present at baseline. The predominant resistance-associated treatment-emergent variants at the time of failure were 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 patient with HCV genotype 4a 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

The persistence of paritaprevir or ombitasvir resistance-associated amino acid substitutions in NS5A or 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 2/3 subjects. NS3 variant D168V was not detected at post-treatment week 48.

Cross-resistance

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

NON-CLINICAL TOXICOLOGY

General Toxicity

Ombitasvir

Ombitasvir was well tolerated without adverse effects in repeated-dose oral toxicity studies in mice (up to 6-months duration), rats (up to 3-months) and dogs (up to 6-months). Maximum achieved ombitasvir plasma exposures in the longest duration studies were at least 20-fold or higher as compared to human exposure at the recommended dose.

Both inactive, major, disproportionate human metabolites of ombitasvir (M29, M36) did not cause adverse effects in 1-month repeat-dose studies at AUC exposures that were ≥ 25-fold relative to anticipated human exposures.

Paritaprevir/ritonavir

Paritaprevir/ritonavir was well tolerated in repeated-dose oral toxicity studies in mice (up to 6-months duration), rats (up to 3-months) and dogs (up to 9-months). The safety margins for studies in the rat, mouse and dog were 22-, 87-, and 310-fold the exposure in human at the recommended dose.

Paritaprevir/ritonavir associated adverse effects were limited to the gallbladder in mice and dogs. In a 6 month study in CD-1 mice the adverse findings included focal erosion/ulceration, inflammation (both acute and chronic active), and epithelial hypertrophy/hyperplasia at paritaprevir exposures of 46-fold the exposure in humans at the recommended dose. Gallbladder findings in the dog were limited to minimal epithelial degeneration/necrosis. No evidence of disruption of the epithelial integrity was noted in the dog, despite achieving exposures of up to 310-fold the exposure in humans at the recommended dose. The severity and character of the gallbladder change in the dog did not progress from the 1-month to the 9 month toxicology study, despite achieving higher exposures in the 9-month study as compared to the 1-month study.

Mutagenicity and Carcinogenicity

Ombitasvir

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in bacterial mutagenicity, human lymphocyte chromosome aberration and *in vivo* mouse micronucleus assays.

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study and a 2-year rat study up to AUC exposures approximately 26- and 16-fold the exposure in humans at the recommended dose.

Paritaprevir/ritonavir

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

Ritonavir was not genotoxic in bacterial mutation assay, mouse lymphoma assay, mouse micronucleus test and chromosomal aberration assay.

Paritaprevir/ritonavir was not carcinogenic in a 6-month transgenic mouse study up to AUC exposures approximately 56- and 6-fold the exposure in humans at the recommended dose. Similarly, paritaprevir/ritonavir was not carcinogenic in a 2-year rat study up to AUC exposures approximately 11- and 6-fold the exposure in humans at the recommended dose.

Use with Ribavirin

Ribavirin was shown to be genotoxic in several *in vitro* and *in vivo* assays. Ribavirin was not carcinogenic in a 6-month p53+/- transgenic mouse study or a 2-year carcinogenicity study in rats. See the Product Monograph for ribavirin for additional information.

Fertility

Ombitasvir

Ombitasvir had no effects on fertility when evaluated in mice up to AUC exposures approximately 26-fold the exposure in humans at the recommended clinical dose.

Paritaprevir/ritonavir

Paritaprevir/ritonavir had no effects on fertility when evaluated in rats up to AUC exposures approximately 6- and 3-fold the exposure in humans at the recommended clinical dose.

Use with Ribavirin

In fertility studies in male animals, ribavirin induced reversible testicular toxicity. Refer to Product Monograph for ribavirin for additional information.

REFERENCES

1. Public Health Agency of Canada. Hepatitis C in Canada: 2005-2010 Surveillance Report. Centre for Communicable Diseases and Infection Control, Infectious Disease Prevention and Control Branch, Public Health Agency of Canada; 2011.

2. Wong T, Lee SS. Hepatitis C: A review for primary care physicians. *Can Med Assoc J* 2006 28 Feb;174(5):649-659.

3. Al Naamani K, Al Sinani S, Deschênes M. Epidemiology and treatment of hepatitis C genotypes 5 and 6. *Can J Gastroenterol* 2013 Jan;27(1):e8-12.

4. Andonov A, Chaudhary RK. Genotyping of Canadian hepatitis C virus isolates by PCR. *J Clin Microbiol* 1994;32:2031-4.

5. Murphy DG, Willems B, Delage G, et al. Hepatitis C virus genotypes in patients and blood donors – Quebec. *Can Commun Dis Rep* 1995;21:129-32.

6. Bernier L, Willems B, Delage G, Murphy DG. Identification of numerous hepatitis C virus genotypes in Montreal, Canada. *J Clin Microbiol* 1996;34:2815-8.

7. Chaudhary R, Tepper M, Eisaadany S, Gully PR. Distribution of hepatitis C virus genotypes in Canada: Results from the LCDC Sentinel Health Unit Surveillance System. *Can J Infect Dis* 1999 Jan;10(1):53-6.

8. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2013. Toronto, ON: Canadian Cancer Society; 2013.

9. Remis R. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007 final report. Public Health Agency of Canada. 2007.

10. Myers RP1, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. *Can J Gastroenterol* 2012 Jun;26(6):359-75.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

[Pr]TECHNIVIE™ (pronounced TEK-ni-vee)

ombitasvir/paritaprevir/ritonavir tablets

Read this carefully before you start taking TECHNIVIE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your doctor about your medical condition and treatment and ask if there is any new information about TECHNIVIE.

Serious Warnings and Precautions

Hepatitis B activity (e.g., inflamed liver) may increase when taking antiviral drugs like TECHNIVIE, sometimes leading to liver failure and death. (See the "To help avoid side effects…" section, *Hepatitis B Reactivation*)

What is TECHNIVIE used for?

- TECHNIVIE treats long-lasting hepatitis C virus (HCV) infection in adults 18 years and older. It treats one kind of HCV infection called HCV genotype 4.
- TECHNIVIE is normally used with ribavirin, but not always. Read the ribavirin patient medication information if your doctor says you should also take ribavirin.

How does TECHNIVIE work?

TECHNIVIE with ribavirin can cure HCV infection in most patients. Cure means HCV is cleared from your blood 3 months after finishing the medicine.

TECHNIVIE has two types of HCV medicines in each tablet. These 2 medicines stop HCV from multiplying in different ways.

Curing HCV infection can help lower the chance you will have problems or die from HCV.

Taking TECHNIVIE does not keep you from getting infected again. Talk with your doctor about ways to avoid getting infected again with HCV.

Can I still pass on HCV to others if I take TECHNIVIE?

Yes you can still pass on HCV to others while you are taking TECHNIVIE. Some ways that HCV can be passed on is by sharing needles or through unprotected sex. Talk with your doctor about ways to avoid passing on HCV infection.

What are the ingredients in TECHNIVIE?

Ombitasvir/paritaprevir/ritonavir tablets

Each tablet has the following medicines: ombitasvir, paritaprevir and ritonavir.

Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, propylene glycol monolaurate, sodium stearyl fumarate, sorbitan monolaurate, vitamin E polyethylene glycol succinate.

Each tablet is covered with the following ingredients that are not medicines: iron oxide red, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide.

The tablets do not contain gluten.

TECHNIVIE comes in the following dosage forms:

Each tablet has 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir.

Do not use TECHNIVIE if:

- your doctor says you should also use ribavirin and you are pregnant or want to become pregnant (or your partner is pregnant or wants to become pregnant). Ribavirin may cause birth defects or death of your unborn baby.
- you are allergic to any of the medicines or other ingredients in TECHNIVIE (see the section "**What are the ingredients in TECHNIVIE?**" to see all the medicines and ingredients).
- your doctor has told you that you have moderate or severe loss of liver function.
- you are taking any of the following medicines or natural substances:
    - alfuzosin hydrochloride (Xatral®)
    - astemizole*
    - bosentan (Tracleer®)
    - carbamazepine (Tegretol®)
    - cisapride*
    - colchicine, for patients that have certain kidney and liver problems
    - dronedarone (Multaq®)
    - efavirenz-containing medicines (Sustiva®, Atripla®)

- ergot containing medicines including:
  - ergonovine*
  - ergotamine tartrate*
  - ergotamine (Bellergal Spacetabs®)
  - dihydroergotamine mesylate (Migranal®)
  - methylergonovine*
- ethinyl estradiol-containing medicines such as those contained in most contraceptive pills and vaginal rings used for contraception
- etravirine (Intelence®)
- fusidic acid (systemic)*
- lovastatin
- lurasidone (Latuda®)
- midazolam (when taken by mouth)
- modafinil (Alertec®)
- nevirapine (Viramune®)
- phenytoin (Dilantin®)
- phenobarbital
- pimozide (Orap®)
- rifampin (Rifadin®, Rifater®, Rofact®)
- salmeterol (Advair Diskus®, Serevent Diskus®)
- sildenafil citrate (Revatio®) for the lung problem, pulmonary artery hypertension (PAH)
- simvastatin
- St. John's Wort (*Hypericum perforatum*) or products containing St. John's Wort
- terfenadine*
- triazolam

*** Drugs not sold in Canada.**

To help avoid side effects and make sure you are using your medicines correctly, talk to your doctor before you take TECHNIVIE. Talk about any health problems you may have, including if you:

- are taking birth control medicines of any kind or using a medicine that has ethinyl estradiol. Ethinyl estradiol is usually found in birth control pills. However, not all birth control pills have ethinyl estradiol. You must not use medicines that have ethinyl estradiol while taking TECHNIVIE. Your doctor will ask you to stop or change to a different type of birth control while you are taking TECHNIVIE.

- have any other medical condition.

- have had a kidney and/or liver transplant.
  - You should not take TECHNIVIE if you are taking everolimus. The dose of everolimus cannot be adjusted to maintain the correct drug levels when given with TECHNIVIE.

- If you are taking tacrolimus, you should talk to your doctor about the risks and benefits of taking TECHNIVIE at the same time and consider:
    - Serious and life-threatening side effects have occurred when taking TECHNIVIE with tacrolimus
    - Your doctor may order blood tests to check tacrolimus levels in your blood at the beginning and during treatment with TECHNIVIE
- Talk with your doctor if you are taking cyclosporine for your transplant. The levels of this medicine can change when taken with TECHNIVIE. Your doctor will choose how much cyclosporine you need to take:
    - with TECHNIVIE.
    - when you have completed TECHNIVIE.
    - if you have to stop taking TECHNIVIE for any reason.

- have liver problems other than HCV infection.
- also have HIV infection.
- are breastfeeding or plan to breastfeed. It is not known if TECHNIVIE passes into your breast milk. You and your doctor should decide if you will take TECHNIVIE or breastfeed. You should not do both.

Hepatitis B Reactivation

Taking antiviral drugs such as TECHNIVIE may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Contact your doctor if:

- you have never been tested for hepatitis B
- you know you have a current hepatitis B infection
- you have had a previous hepatitis B infection

Your healthcare professional may do blood tests:

- before hepatitis C treatment
- to see the hepatitis B levels in your blood
- and may order hepatitis B treatment

Pregnancy and Birth Control

- Females must have a negative pregnancy test before starting TECHNIVIE and ribavirin, every month while on the medicine, and for 6 months after stopping them.
- You or your partner should not become pregnant while taking TECHNIVIE with ribavirin and for 6 months after you have stopped taking them.
- You and your partner must use 2 kinds of birth control while taking TECHNIVIE and ribavirin and for 6 months after you have stopped taking them.
- Talk to your doctor about the kind of birth control that you can use.
- If you or your partner becomes pregnant while taking TECHNIVIE and ribavirin or within 6 months after you stop taking them, tell your doctor right away.

Other warnings you should know about:

TECHNIVIE may cause severe liver problems, especially in people with advanced cirrhosis (liver scarring). These severe liver problems can lead to the need for a liver transplant, or can lead to death.

Rises in liver tests have occurred when TECHNIVIE was taken in studies. Contact your doctor right away if you have symptoms like those listed below since these may mean you have a serious problem with your liver:

- loss of appetite (do not feel like eating),
- stomachache,
- swelling of your stomach area,
- nausea (feeling sick in the stomach),
- vomiting,
- feeling tired or weak,
- yellowing of the skin and eyes,
- confusion
- dark urine and pale stool.

It is not known if taking TECHNIVIE is safe or will work in children under 18 years of age.

Your doctor may do blood tests before you start taking, and while you are on your medicines. This is to help check if the medicines are working for you.

Tell your doctor all the medicines, drugs, vitamins and minerals, natural supplements or alternative medicines you are already taking. Also tell your doctor if you stop any of these or start any new ones.

Do not take TECHNIVIE with the following medicines:

- other ritonavir-containing medicines (Norvir®, Kaletra®). When co-administered with TECHNIVIE, atazanavir or darunavir should be taken without ritonavir.
- amiodarone (Cordarone®)
- alfentanil
- disopyramide (Rythmodan®)
- everolimus (Affinitor®, Affinitor® Disperz)
- fentanyl (Abstral®, Duragesic®)
- flecainide
- lidocaine (systemic)
- propafenone (Rythmol®)
- quetiapine (Seroquel®)
- quinidine
- rilpivirine (Edurant®, Complera®)
- sirolimus (Rapamune®)

The following medicines may interact with TECHNIVIE:

- alprazolam (Xanax®)
- amlodipine (Norvasc®)
- atazanavir (Reyataz®)
- atorvastatin (Lipitor®)
- candesartan (Atacand®/Atacand® Plus)
- carisoprodol*
- cyclobenzaprine
- cyclosporine (Neoral®, Sandimmune®)
- darunavir (Prezista®)
- diazepam (Valium®)
- digoxin (Lanoxin®)
- diltiazem (Cardizem® CD)
- fluticasone (Advair®, Flonase®, Flovent Diskus®, Flovent HFA®)
- fluvastatin (Lescol®)
- furosemide (Lasix®)
- hydrocodone (Hycodan®, Novahistex®, Novahistine ®, Tussionex®)
- itraconazole (Sporanox®)
- ketoconazole (Nizoral®)
- losartan (Cozaar®/Hyzaar®)
- nifedipine (Adalat® XL)
- omeprazole (Losec®)
- pitavastatin*
- posaconazole (Posanol®)
- pravastatin (Pravachol®)
- rosuvastatin (Crestor®)
- tacrolimus (Prograf®)

- valsartan (Diovan®/ Diovan® HCT)
- verapamil (Isoptin® SR)
- voriconazole (Vfend®)
- warfarin (Coumadin®)

*** Drugs not sold in Canada.**

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Keep a list of all the medicines you take. Show it to your doctor and pharmacist when you get a new medicine or stop a medicine.

If you change or stop one of your other medicines while you are taking TECHNIVIE, ask your healthcare provider about changing back when you are finished taking TECHNIVIE.

How to take TECHNIVIE

- Take TECHNIVIE exactly as your doctor tells you. Do not change your dose or stop unless your doctor tells you to.
- Take TECHNIVIE at about the same time every day with food. The type of food is not important.
- Swallow TECHNIVIE tablets whole with water or another liquid if needed.
- Do not chew, break, or crush TECHNIVIE tablets.

Usual adult dose:

- Every day in the morning, take two TECHNIVIE tablets.
- TECHNIVIE is taken for 12 weeks.
- If your doctor has also prescribed ribavirin, your doctor will provide you dosage directions for the ribavirin.

Overdose:

If you think you have taken too much TECHNIVIE contact your doctor or pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if you do not have symptoms.

Missed Dose:

- If you miss a dose of TECHNIVIE tablets and it is:

- less than 12 hours from the time you usually take TECHNIVIE, you should take the missed dose with food as soon as possible. Then take your next dose at your usual time.

- more than 12 hours from the time you usually take TECHNIVIE, you should 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.

What are possible side effects from using TECHNIVIE?

If your side effect is not listed here, contact your healthcare provider. Also see **Other warnings you should know about**.

Common side effects of TECHNIVIE when used with ribavirin:

- headache
- itching
- feeling tired or weak
- trouble sleeping
- too much of a normal substance called bilirubin in the blood that could cause yellowing of the skin and eyes

Other side effects:

You could also have an allergic reaction. Symptoms of allergic reactions could be swelling of the mouth, throat, hands and feet, trouble breathing, rash, and itching.

If you have side effect that is not listed here or becomes bad enough to get in the way of your daily tasks, tell your doctor.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

NOTE: Contact your doctor if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2 and 30°C. Keep away from moisture.

Keep TECHNIVIE out of the reach and sight of children.

If you want more information about TECHNIVIE:

- Talk to your doctor
- Find the most recent version of the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website abbvie.ca, or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation

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Abstral, Adalat XL, Advair, Advair Diskus, Affinitor, Affinitor Disperz, Alertec, Atacand, Atacand Plus, Atripla, Bellergal Spacetabs, Cardizem CD, Complera, Cordarone,Coumadin, Cozaar, Crestor, Dilantin, Diovan, Diovan HCT, Duragesic, Edurant, Flonase, Flovent Diskus, Flovent HFA, Hycodan, Hyzaar, Intelence, Isoptin SR, Lanoxin, Lasix, Latuda, Lescol, Lipitor, Losec, Migranal, Multaq, Neoral, Nizoral, Norvasc, Novahistex, Novahistine, Orap, Posanol, Pravachol, Prezista, Prograf, Rapamune, Revatio, Reyataz, Rifadin, Rifater, Rofact, Rythmodan,

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