TECHNIVIE - ombitasvir and paritaprevir and ritonavir
AbbVie Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TECHNIVIE safely and effectively. See full prescribing information for TECHNIVIE.

TECHNIVIE (ombitasvir, paritaprevir and ritonavir) tablets, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage, Removed-Limitations of Use (1)	10/2015
Dosage and Administration, Testing Prior to Initiation of TECHNIVIE (2.1)	10/2015
Dosage and Administration, Recommended Dosage in Adults (2.2)	10/2015
Dosage and Administration, Dosage in Patients with Hepatic Impairment (2.3)	10/2015
Contraindications (4)	10/2015
Warnings and Precautions (5.1)	10/2015

INDICATIONS AND USAGE

TECHNIVIE is a fixed-dose combination of ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, and ritonavir, a CYP3A inhibitor and is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis. (1)

DOSAGE AND ADMINISTRATION

- Testing Prior to Initiation: Assess baseline hepatic laboratory and clinical parameters. (2.1)
- Recommended dosage: Two tablets taken orally once daily (in the morning) with a meal without regard to fat or calorie content. TECHNIVIE is recommended to be used in combination with ribavirin. (2.2)

Patient Population	Treatment	Duration
Genotype 4 without cirrhosis	TECHNIVIE + ribavirin*	12 weeks
*TECHNIVIE administered without ribavirin for 12 weeks may be considered for treatment-naïve patients who cannot take or tolerate ribavirin *[see Microbiology (12.4) and Clinical Studies (14)]*.		

DOSAGE FORMS AND STRENGTHS

Tablets: 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir. (3)

CONTRAINDICATIONS

- The contraindications to ribavirin also apply to this combination regimen. (4)
- Patients with moderate to severe hepatic impairment. (4, 5.1, 8.6, 12.3)
- Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate and strong inducers of CYP3A. (4)
- Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome). (4)

WARNINGS AND PRECAUTIONS

- Hepatic Decompensation and Hepatic Failure in Patient with Cirrhosis: Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported mostly in patients with advanced cirrhosis. Discontinue treatment in patients who develop evidence of hepatic decompensation. (5.1)
- ALT Elevations: Discontinue ethinyl estradiol-containing medications prior to starting TECHNIVIE (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations on TECHNIVIE, monitor closely and follow recommendations in full prescribing information. (5.2)
- Risks Associated With Ribavirin Combination Treatment: The warnings and precautions for ribavirin also apply to this combination regimen. (5.3)
- Drug Interactions: The concomitant use of TECHNIVIE and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of TECHNIVIE. (5.4)

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence greater than 10% of subjects, all grades) observed with treatment with ombitasvir, paritaprevir and ritonavir with ribavirin for 12 weeks were asthenia, fatigue, nausea and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of TECHNIVIE can alter the plasma concentrations of some drugs and some drugs may alter the plasma concentrations of TECHNIVIE. The potential for drug-drug interactions must be considered before and during treatment. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.4, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 02/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TECHNIVIE is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of TECHNIVIE

Prior to initiation of TECHNIVIE, assess baseline hepatic laboratory and clinical parameters*[see Contraindications (4) and Warnings and Precautions (5.1 and 5.2)]*.

2.2 Recommended Dosage in Adults

TECHNIVIE is ombitasvir, paritaprevir and ritonavir fixed dose combination tablets.

The recommended dosage of TECHNIVIE is two tablets taken orally once daily (in the morning). Take TECHNIVIE with a meal without regard to fat or calorie content *[see Clinical Pharmacology (12.3)]*.

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

Table 1 shows the recommended TECHNIVIE treatment regimen and duration for HCV genotype 4 patients without cirrhosis.

Table 1. Treatment Regimen and Duration for Patients with HCV Genotype 4 without Cirrhosis

Patient Population	Treatment	Duration
Genotype 4 without cirrhosis	TECHNIVIE + ribavirin*	12 weeks
*TECHNIVIE administered without RBV for 12 weeks may be considered for treatment-naïve patients who cannot take or tolerate ribavirin *[see Microbiology (12.4) and Clinical Studies (14)]*.		

2.3 Dosage in Patients with Hepatic Impairment

TECHNIVIE is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C)*[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

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.

4 CONTRAINDICATIONS

- The contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- TECHNIVIE is contraindicated:
  - In patients with moderate to severe hepatic impairment (Child-Pugh B and C) due to risk of potential toxicity *[see Warnings and Precautions (5.1), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.
  - With drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - With drugs that are moderate or strong inducers of CYP3A and may lead to reduced efficacy of TECHNIVIE.
  - In patients with known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome).

Table 2 lists drugs that are contraindicated with TECHNIVIE *[see Drug Interactions (7)]*.

Table 2. Drugs that are Contraindicated with TECHNIVIE

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCl	Potential for hypotension.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
Antimycobacterial	Rifampin	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives	Potential for ALT elevations *[see Warnings and Precautions (5.2)]*.
Herbal Product	St. John’s Wort *(Hypericum perforatum)*	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of TECHNIVIE.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.

Neuroleptics	Pimozide	Potential for cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor	Efavirenz	Co-administration of efavirenz based regimens with paritaprevir, ritonavir was poorly tolerated and resulted in liver enzyme elevations.
Phosphodiesterase-5 (PDE5) inhibitor	Sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)	There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Sedatives/hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with TECHNIVIE may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

5 WARNINGS AND PRECAUTIONS

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

TECHNIVIE is not indicated in patients with cirrhosis.

Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported postmarketing in patients treated with ombitasvir, paritaprevir, ritonavir with and without dasabuvir and with and without ribavirin. Most patients with these severe outcomes had evidence of advanced 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 rising direct serum bilirubin levels without ALT elevations in association with clinical signs and symptoms of hepatic decompensation. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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) *[see Contraindications (4), Adverse Reactions (6.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

5.2 Increased Risk of ALT Elevations

During clinical trials with ombitasvir, paritaprevir and ritonavir with or without dasabuvir and with or without ribavirin, elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of subjects *[see Adverse Reactions (6.1)]*. ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment, and declined within two to eight weeks of onset with continued dosing.

These ALT elevations were significantly more frequent in female subjects who were using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches or contraceptive vaginal rings. Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with TECHNIVIE *[see Contraindications (4)]*. Alternative 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.

Women 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. Due to the limited number of subjects taking these other estrogens in clinical studies, caution is warranted for co-administration with TECHNIVIE *[see Adverse Reactions (6.1)]*.

Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. If ALT is found to be elevated above baseline levels, it should be repeated and monitored closely:

- Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces.
- Consider discontinuing TECHNIVIE if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue TECHNIVIE if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or INR.

5.3 Risks Associated With Ribavirin Combination Treatment

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

5.4 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of TECHNIVIE and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of TECHNIVIE and possible development of resistance
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs or components of TECHNIVIE.

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during TECHNIVIE therapy; review concomitant medications during TECHNIVIE therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see Contraindications (4) and Drug Interactions (7)]*.

5.5 Risk of HIV-1 Protease Inhibitor Drug Resistance in HCV/HIV-1 Co-infected Patients

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.

6 ADVERSE REACTIONS

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

The following adverse reaction is described below and elsewhere in the labeling:

- Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis *[see Warnings and Precautions (5.1)]*
- Increased Risk of ALT Elevations *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

The safety assessment of TECHNIVIE is based on data from a clinical study that included 135 HCV genotype 4-infected subjects without cirrhosis, 91 who received ombitasvir 25 mg, paritaprevir 150 mg and ritonavir 100 mg (administered as one ombitasvir 25 mg tablet, three paritaprevir 50 mg tablets and one ritonavir 100 mg capsule) once daily with ribavirin for 12 weeks and 44 subjects without cirrhosis who received ombitasvir 25 mg, paritaprevir 150 mg, and ritonavir 100 mg (administered as one ombitasvir 25 mg tablet, three paritaprevir 50 mg tablets and one ritonavir 100 mg capsule) once daily without ribavirin for 12 weeks (PEARL-I).

Adverse reactions that occurred in subjects treated with ombitasvir, paritaprevir and ritonavir with or without ribavirin for 12 weeks are listed in Table 3. The majority of adverse reactions in PEARL-I were mild in severity. None of the subjects who received ombitasvir, paritaprevir and ritonavir with ribavirin experienced a serious adverse reaction. None of the subjects receiving ombitasvir, paritaprevir and ritonavir with or without ribavirin discontinued treatment due to an adverse reaction.

Table 3. Selected Adverse Reactions (All Grades) with ≥5% Frequency Reported in Subjects Treated with Ombitasvir, Paritaprevir and Ritonavir with or without Ribavirin for 12 Weeks

	PEARL-I	
Adverse Reaction	Ombitasvir, paritaprevir, ritonavir + RBV 12 Weeks N = 91 %	Ombitasvir, paritaprevir, ritonavir 12 Weeks N = 44 %
Asthenia	29	25
Fatigue	15	7
Nausea	14	9
Insomnia	13	5
Pruritus*	7	5
Skin reactions[$,#]	7	5

*Grouped term ‘pruritus’ includes the preferred terms pruritus and pruritus generalized.
[$]Grouped term ‘skin reactions’ includes the preferred terms rash, erythema, eczema, rash maculo-papular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, rash generalized, dermatitis allergic, dermatitis contact, exfoliative rash, photosensitivity reaction, psoriasis, skin reaction, ulcer and urticaria.
[#]The majority of events were graded as mild in severity. There were no serious events or severe cutaneous reactions, such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) or drug rash with eosinophilia and systemic symptoms (DRESS).

Laboratory Abnormalities

Serum ALT Elevations

None of the 135 HCV GT4 infected subjects treated with TECHNIVIE experienced post-baseline serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment *[see Warnings and Precautions (5.2)]*.

Serum Bilirubin Elevations

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

Anemia/Decreased Hemoglobin

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

6.2 Post-Marketing Experience

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 (5.1)]*.

7 DRUG INTERACTIONS

See also Contraindications (4), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3).

7.1 Potential for TECHNIVIE to Affect Other Drugs

Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir and ritonavir are inhibitors of BCRP and P-gp. Ritonavir is an inhibitor of CYP3A4. Co-administration of TECHNIVIE with drugs that are substrates of CYP3A, P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

7.2 Potential for Other Drugs to Affect One or More Components of TECHNIVIE

Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes. Co-administration of TECHNIVIE with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Ombitasvir is primarily metabolized via amide hydrolysis while CYP enzymes play a minor role in its metabolism. 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 the plasma concentrations of the various components of TECHNIVIE.

7.3 Established and Other Potential Drug Interactions

If dosage adjustments of concomitant medications are made due to treatment with TECHNIVIE, dosages should be re-adjusted after administration of TECHNIVIE is completed. Dosage adjustment is not required for TECHNIVIE.

Table 4 provides the effect of co-administration of TECHNIVIE on concentrations of concomitant drugs and the effect of concomitant drugs on the various components of TECHNIVIE. See *Contraindications (4)* for drugs that are contraindicated with TECHNIVIE. Refer to the ritonavir prescribing information for other potentially significant drug interactions with ritonavir.

Table 4. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
ANGIOTENSIN RECEPTOR BLOCKERS e.g.		
valsartan*, losartan*, candesartan*	↑ angiotensin receptor blockers	Decrease the dose of the angiotensin receptor blockers and monitor patients for signs and symptoms of hypotension and/or worsening renal function. If such events occur, consider further dose reduction of the angiotensin receptor blocker or switching to an alternative to the angiotensin receptor blocker.
ANTIARRHYTHMICS		
digoxin	↑ digoxin	Decrease digoxin dose by 30-50%. Appropriate monitoring of serum

		digoxin levels is recommended.
amiodarone*, bepridil*, disopyramide*, flecainide*, lidocaine (systemic)*, mexiletine*, propafenone*, quinidine*	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with TECHNIVIE.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole	When TECHNIVIE is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg per day.
voriconazole*	↓ voriconazole	Co-administration of TECHNIVIE with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
ANTIPSYCHOTICS		
quetiapine*	↑ quetiapine	• Initiation of TECHNIVIE in patients taking quetiapine: Consider alternative anti-HCV therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6th of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. • Initiation of quetiapine in patients taking TECHNIVIE: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
CALCIUM CHANNEL BLOCKERS		
amlodipine, nifedipine*, diltiazem*, verapamil*	↑ calcium channel blockers	Decrease the dose of the calcium channel blocker. The dose of amlodipine should be decreased by at least 50%. Clinical monitoring of patients is recommended for edema and/or signs and symptoms of hypotension. If such events occur, consider further dose reduction of the calcium channel blocker or switching to an alternative to the calcium channel blocker.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone*	↑ fluticasone	Concomitant use of TECHNIVIE with inhaled or nasal fluticasone may reduce serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long term use.
DIURETICS		
furosemide	↑ furosemide (C_{max})	Clinical monitoring of patients is recommended and therapy should be individualized based on patient's response.
HIV-ANTIVIRAL AGENTS		
atazanavir or atazanavir/ritonavir	↑ paritaprevir	Co-administration of TECHNIVIE with atazanavir or atazanavir/ritonavir is not recommended.
darunavir/ritonavir	↓ darunavir (C_{trough})	When co-administered with TECHNIVIE, darunavir 800 mg (without ritonavir) should be taken at the same time as TECHNIVIE.
lopinavir/ritonavir	↑ paritaprevir	Co-administration of TECHNIVIE with lopinavir/ritonavir is not recommended.
rilpivirine	↑ rilpivirine	Co-administration of TECHNIVIE with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine.
HMG CoA REDUCTASE INHIBITORS		
pravastatin	↑ pravastatin	When TECHNIVIE is co-administered with pravastatin, the dose of pravastatin should not exceed 40 mg per day.
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine	When initiating therapy with TECHNIVIE, reduce cyclosporine dose to 1/5th of the patient's current cyclosporine dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Upon completion of TECHNIVIE therapy, the appropriate time to resume pre-

		TECHNIVIE dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
tacrolimus	↑ tacrolimus	When initiating therapy with TECHNIVIE, the dose of tacrolimus needs to be reduced. Do not administer tacrolimus on the day TECHNIVIE is initiated. Beginning the day after TECHNIVIE is initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. Typical tacrolimus dosing is 0.5 mg every 7 days. Measure tacrolimus blood concentrations and adjust dose or dosing frequency to determine subsequent dose modifications. Upon completion of TECHNIVIE therapy, the appropriate time to resume pre-TECHNIVIE dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus related side effects is recommended.
LONG ACTING BETA-ADRENOCEPTOR AGONIST		
salmeterol*	↑ salmeterol	Concurrent administration of TECHNIVIE and salmeterol is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS		
buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine	No dose adjustment of buprenorphine/naloxone is required upon co-administration with TECHNIVIE. Patients should be closely monitored for sedation and cognitive effects.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.
SEDATIVES/HYPNOTICS		
alprazolam	↑ alprazolam	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.

*Not studied.
See Clinical Pharmacology, Tables 5 and 6.
The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC) (↑ = *increase of more than 20%,* ↓ = *decrease of more than 20%).*

7.4 Drugs without Clinically Significant Interactions with TECHNIVIE

No dosage adjustments are recommended when TECHNIVIE is co-administered with the following medications: duloxetine, emtricitabine/tenofovir disoproxil fumarate, escitalopram, gemfibrozil, methadone, progestin only contraceptives, raltegravir, rosuvastatin, warfarin and zolpidem.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

Adequate and well controlled studies with TECHNIVIE have not been conducted in pregnant women. In animal reproduction studies, no evidence of teratogenicity was observed with the administration of ombitasvir (mice and rabbits), paritaprevir or ritonavir (mice and rats) at exposures higher than the recommended clinical dose [see Data]. Because animal reproduction studies are not always predictive of human response, TECHNIVIE should be used during pregnancy only if clearly needed.

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 prescribing information for more information on use of ribavirin in males and females of child-bearing potential.

Data

Animal data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals treated throughout pregnancy with ombitasvir and its major inactive human metabolites (M29, M36), paritaprevir or ritonavir. For ombitasvir, the highest dose tested produced exposures approximately 29-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26-fold the exposures in humans at the recommended clinical dose. For paritaprevir, ritonavir, the highest doses

tested produced exposures approximately 143-fold (mouse) or 12-fold (rat) the exposures of paritaprevir in humans at the recommended clinical dose.

8.3 Nursing Mothers

It is not known whether any of the components of TECHNIVIE or their metabolites are present in human milk. Unchanged ombitasvir, paritaprevir and its hydrolysis product M13 were the predominant components observed in the milk of lactating rats, without effect on nursing pups.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TECHNIVIE and any potential adverse effects on the breastfed child from TECHNIVIE or from the underlying maternal condition.

When TECHNIVIE is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen (see prescribing information for ribavirin).

8.4 Pediatric Use

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

8.5 Geriatric Use

No dosage adjustment of TECHNIVIE is warranted in geriatric patients. Clinical study PEARL-I did not include sufficient numbers of patients older than 65 years of age to assess safety or efficacy, or to determine if they responded differently than younger patients.

8.6 Hepatic Impairment

No dosage 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 Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment of TECHNIVIE is required in patients with mild, moderate or severe renal impairment. TECHNIVIE has not been studied in patients on dialysis. For patients that require ribavirin, refer to the ribavirin prescribing information for information regarding use in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

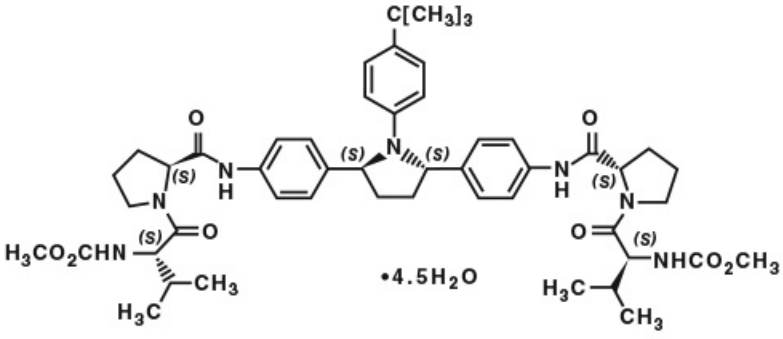
11 DESCRIPTION

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

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

Ombitasvir

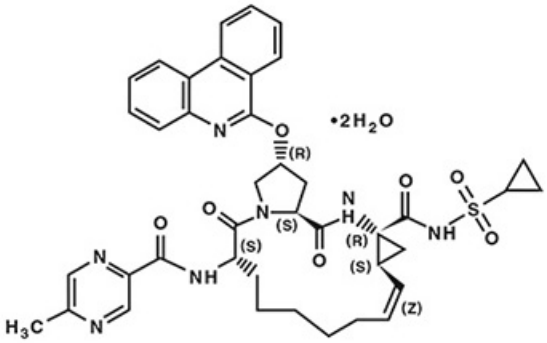
The chemical name of ombitasvir is Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate. The molecular formula is $C_{50}H_{67}N_7O_8 \cdot 4.5H_2O$ (hydrate) and the molecular weight for the drug substance is 975.20 (hydrate). The drug substance is white to light yellow to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. Ombitasvir has the following molecular structure:



Paritaprevir

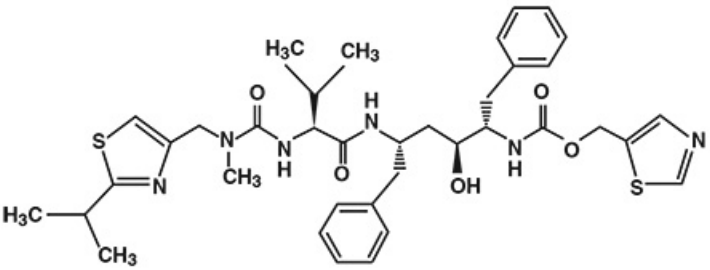
The chemical name of paritaprevir is (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-

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. The molecular formula is $C_{40}H_{43}N_7O_7S•2H_2O$ (dihydrate) and the molecular weight for the drug substance is 801.91 (dihydrate). The drug substance is white to off-white powder with very low water solubility. Paritaprevir has the following molecular structure:



Ritonavir

The chemical name of ritonavir is [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. The molecular formula is $C_{37}H_{48}N_6O_5S_2$ and the molecular weight for the drug substance is 720.95. The drug substance is white to off white to light tan powder practically insoluble in water and freely soluble in methanol and ethanol. Ritonavir has the following molecular structure:



Ombitasvir, Paritaprevir, Ritonavir Fixed-Dose Combination Tablets

Ombitasvir, paritaprevir and ritonavir film-coated tablets are co-formulated immediate release tablets. The tablet contains copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and iron oxide red. The strength for the tablet is 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TECHNIVIE combines two direct-acting hepatitis C virus antiviral agents with distinct mechanisms of action *[see Microbiology (12.4)]*.

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).

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of a combination of ombitasvir, paritaprevir and ritonavir plus 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.

12.3 Pharmacokinetics

Absorption

Ombitasvir, paritaprevir and ritonavir were absorbed after oral administration with mean T_{max} of approximately 4 to 5 hours. While ombitasvir exposures increased in a dose proportional manner, paritaprevir and ritonavir exposures increased in a more than dose proportional manner. Accumulation is minimal for ombitasvir and approximately 1.5- to 2-fold for ritonavir and paritaprevir. Steady state exposures are achieved after approximately 12 days of dosing.

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

Based on the population pharmacokinetic analysis, the median steady-state AUC_{0-24} for ombitasvir, paritaprevir and ritonavir were 1239, 2276 and 6072 ng·hr/mL, respectively, when administered to HCV genotype 4-infected subjects. Median steady-state C_{max} for ombitasvir, paritaprevir, and ritonavir were 82, 194 and 543 ng/mL, respectively, when administered to HCV genotype 4-infected subjects.

Effects of Food on Oral Absorption

Relative to fasting conditions, administration of ombitasvir, paritaprevir and ritonavir with a moderate fat meal (approximately 600 Kcal, 20-30% calories from fat) increased the mean AUC by 82%, 211% and 49%, respectively.

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

Ombitasvir, paritaprevir, and ritonavir should always be administered with a meal.

Distribution

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

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

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

Metabolism

Ombitasvir: Ombitasvir is predominantly metabolized by amide hydrolysis followed by oxidative metabolism.

Paritaprevir: Paritaprevir is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

Ritonavir: Ritonavir is predominantly metabolized by CYP3A, and to a lesser extent by CYP2D6.

Elimination

Ombitasvir: Following a single dose administration of ^{14}C-ombitasvir, 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 single dose administration of ^{14}C-paritaprevir co-dosed with 100 mg of 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. The mean plasma half-life of paritaprevir was approximately 5.5 hours.

Ritonavir: Following dosing of ritonavir with ombitasvir and paritaprevir, mean plasma half-life of ritonavir was approximately 4 hours. Following a single 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).

Specific Populations

Hepatic Impairment

The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and another antiviral drug were evaluated in non-HCV infected subjects with mild hepatic impairment (Child-Pugh A; score of 5-6), moderate hepatic impairment (Child-Pugh B, score of 7-9) and severe hepatic impairment (Child-Pugh C, score of 10-15).

Relative to subjects with normal hepatic function, ombitasvir, paritaprevir and ritonavir mean AUC values decreased by 8%, 29% and 34%, respectively, in subjects with mild hepatic impairment.

Relative to subjects with normal hepatic function, ombitasvir and ritonavir mean AUC values decreased by 30% and 30%, respectively and paritaprevir mean AUC values increased by 62% in subjects with moderate hepatic impairment.

Relative to subjects with normal hepatic function, paritaprevir and ritonavir mean AUC values increased by 945% and 13% respectively and ombitasvir mean AUC values decreased by 54% in subjects with severe hepatic impairment *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

Renal Impairment

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

Overall, changes in exposure of ombitasvir, paritaprevir, and ritonavir in non-HCV infected subjects with mild-, moderate- and severe renal impairment are not expected to be clinically relevant. Pharmacokinetic data are not available on the use of TECHNIVIE in non-HCV infected subjects with End Stage Renal Disease (ESRD).

Relative to subjects with normal renal function, ritonavir AUC values increased by 40%, while ombitasvir and paritaprevir AUC

values were unchanged in subjects with mild renal impairment.

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

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

Pediatric Population

The pharmacokinetics of TECHNIVIE in pediatric patients less than 18 years of age has not been established *[see Use in Specific Populations (8.4)]*.

Sex

No dosage adjustment is recommended based on sex or body weight.

Race/Ethnicity

No dosage adjustment is recommended based on race or ethnicity.

Age

No dosage adjustment is recommended in geriatric patients *[see Use in Specific Populations (8.5)]*.

Drug Interactions

See also Contraindications (4), Warnings and Precautions (5.4), Drug Interactions (7)

The effects of drugs discussed in Table 4 on the exposures of the individual components of TECHNIVIE are shown in Table 5. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 5. 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}
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)
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)
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)
			ritonavir	0.85 (0.72, 0.99)	0.97 (0.84, 1.13)	1.45 (1.29, 1.64)
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
Cyclosporine	10 single dose[c]	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)

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)
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)
Ethinyl estradiol/ Norgestimate	Ethinyl estradiol 0.035 and Norgestimate 0.25 once daily	7[d]	ombitasvir	1.05 (0.81, 1.35)	0.97 (0.81, 1.15)	0.96 (0.88, 1.12)
			paritaprevir	0.70 (0.40, 1.21)	0.66 (0.42, 1.04)	0.87 (0.67, 1.14)
			ritonavir	0.80 (0.53, 1.21)	0.71 (0.54, 0.94)	0.79 (0.68, 0.93)
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)
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
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[e]	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)
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)
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)
Rilpivirine[a]	25 once daily (morning)[f]	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)
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	0.884 (0.76, 0.93)	0.89 (0.85, 0.93)	1.04 (0.96, 1.13)

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. 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.
d. Data shown is combined data for ombitasvir/paritaprevir/ritonavir with (N=3) and without (N=4) dasabuvir.
e. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of ombitasvir/paritaprevir/ritonavir.
f. Similar changes were observed when rilpivirine was dosed in the evening with food or 4 hours after food.
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 6 summarizes the effects of TECHNIVIE on the pharmacokinetics of co-administered drugs which showed clinically relevant changes. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 6. 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}
Alprazolam[a]	0.5 single dose	12	1.09 (1.03, 1.15)	1.34 (1.15, 1.55)	NA
Amlodipine[a]	5 single dose	14	1.26 (1.11, 1.44)	2.57 (2.31, 2.86)	NA
Atazanavir[b]	300 once daily	11	0.90 (0.83, 0.97)	0.93 (0.85, 1.02)	0.81 (0.72, 0.91)
Buprenorphine	Buprenorphine: 4 to 24 once daily and Naloxone: 1 to 6 once daily	11	1.19 (1.01, 1.40)[c]	1.51 (1.27, 1.78)[c]	1.65 (1.30, 2.08)[c]
Norbuprenorphine			1.82 (1.41, 2.36)[c]	2.11 (1.65, 2.70)[c]	1.87 (1.48, 2.36)[c]
Naloxone			0.99 (0.84, 1.16)[c]	1.11 (0.91, 1.37)[c]	NA
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)
Cyclosporine	10 single dose[d]	12	0.83 (0.72, 0.94)[c]	4.28 (3.66, 5.01)[c]	12.85 (10.61, 15.55)[c]
Darunavir[b]	800 once daily	9	0.99	0.92	0.74

			(0.92, 1.08)	(0.84, 1.00)	(0.63, 0.88)
Digoxin	0.5 single dose	11	1.58 (1.43-1.73)	1.36 (1.21-1.53)	1.24 (1.07-1.43)
Ethinyl Estradiol[e]	Ethinyl estradiol 0.035 and Norgestimate 0.25 once daily	8	1.16 (0.90, 1.50)	1.06 (0.96, 1.17)	1.12 (0.94, 1.33)
Norelgestromin[e]		9	2.01 (1.77, 2.29)	2.60 (2.30, 2.95)	3.11 (2.51, 3.85)
Norgestrel[e]		9	2.26 (1.91, 2.67)	2.54 (2.09, 3.09)	2.93 (2.39, 3.57)
Furosemide[a]	20 single dose	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	NA
Ketoconazole	400 once daily	12	1.10 (1.05, 1.16)	2.05 (1.93, 2.18)	NA
Lopinavir/ritonavir[f]	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[f,g]	800/200 once daily	12	1.05 (0.95, 1.17)	1.17 (1.09, 1.26)	3.50 (2.69, 4.56)
Omeprazole	40 once daily	12	0.48 (0.29, 0.78)	0.46 (0.27, 0.77)	NA
Pravastatin	10 once daily	10	1.43 (1.09, 1.88)	1.76 (1.46, 2.13)	NA
Rilpivirine[a]	25 once daily (morning)[h]	8	2.55 (2.08, 3.12)	3.25 (2.80, 3.77)	3.62 (3.12, 4.21)
Tacrolimus	0.5 single dose[i]	11	4.27 (3.49, 5.22)[c]	85.81 (67.88, 108.49)[c]	24.61 (19.69, 30.77)[c]

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. Dose normalized parameters reported.
d. 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.
e. Data shown is combined data for ombitasvir/paritaprevir/ritonavir with (N=3) and without (N=6) dasabuvir.
f. Lopinavir parameters are reported.
g. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of ombitasvir/paritaprevir/ritonavir.
h. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.
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.

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.

12.4 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 an 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.

Antiviral Activity

Ombitasvir

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

Paritaprevir

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

In HCV replicon cell culture assays, ritonavir did not exhibit a direct antiviral effect and the presence of ritonavir did not affect the antiviral activity of paritaprevir.

Resistance

In Cell Culture

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

For ombitasvir, in an HCV genotype 4a replicon, NS5A substitution L28V reduced ombitasvir antiviral activity by 21-fold. In an HCV genotype 4d replicon, substitutions L28V alone and L28V in combination with T58S reduced ombitasvir antiviral activity by 310- and 760-fold, respectively. Ombitasvir activity against an HCV genotype 4d replicon was not reduced by a T58P polymorphism, which represents the consensus sequence observed at this position for HCV genotype 4a and 4d subjects in PEARL-I.

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

In Clinical Studies

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

Persistence of Resistance-Associated Substitutions

The persistence of ombitasvir or paritaprevir resistance-associated amino acid substitutions in NS5A or NS3, respectively, in HCV genotype 4 has not been studied. In HCV genotype 1, persistence of ombitasvir and paritaprevir resistance-associated substitutions through 24 or 48 weeks post-treatment has been observed in subjects who experienced virologic failure with ombitasvir- and paritaprevir-containing regimens. The long-term clinical impact of the emergence or persistence of virus containing ombitasvir or paritaprevir resistance-associated substitutions is unknown.

Effect of Baseline HCV Polymorphisms on Treatment Response

Phylogenetic analysis of HCV sequences from genotype 4-infected subjects in the clinical study PEARL-I, identified 7 HCV genotype 4 subtypes (4a, 4b, 4c, 4d, 4f, 4g/4k, 4o). Most subjects were infected with either subtype 4a (38%) or 4d (52%); 1 to 7 subjects were infected with each of the other genotype 4 subtypes. Among subjects enrolled at U.S. study sites, 16/18 (89%) were infected with HCV subtype 4a; one subject each was infected with subtype 4c or 4d. Three subjects who experienced virologic failure with the regimen containing paritaprevir/ritonavir and ombitasvir without ribavirin were infected with HCV subtype 4d.

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

Cross-resistance

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Ombitasvir

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (150 mg per kg per day).

The carcinogenicity study of ombitasvir in rats is ongoing.

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

Paritaprevir, ritonavir

Paritaprevir, ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (300/30 mg per kg per day). Similarly, paritaprevir, ritonavir was not carcinogenic in a 2-year rat study up to the highest dose tested (300/30 mg per kg per day), resulting in paritaprevir exposures approximately 11-fold higher than those in humans at 150 mg.

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

TECHNIVIE is administered with ribavirin. Refer to the prescribing information for ribavirin for information on carcinogenesis and mutagenesis.

Impairment of Fertility

Ombitasvir

Ombitasvir had no effects on embryo-fetal viability or on fertility when evaluated in mice up to the highest dose of 200 mg per kg per day. Ombitasvir exposures at this dose were approximately 26-fold the exposure in humans at the recommended clinical dose.

Paritaprevir, ritonavir

Paritaprevir, ritonavir had no effects on embryo-fetal viability or on fertility when evaluated in rats up to the highest dose of 300/30 mg per kg per day. Paritaprevir exposures at this dose were approximately 3- to 8-fold the exposure in humans at the recommended clinical dose.

TECHNIVIE is administered with ribavirin. Refer to the prescribing information for ribavirin for information on Impairment of Fertility.

14 CLINICAL STUDIES

14.1 Clinical Trial Results in Adults with Chronic GT4 HCV Infection without Cirrhosis

The efficacy and safety of TECHNIVIE was evaluated in a single clinical trial in subjects with genotype 4 (GT4) chronic hepatitis virus (HCV) infection. PEARL-I was a randomized, global, multicenter, open-label trial that enrolled 135 adults with HCV GT4 infection without cirrhosis who were either treatment-naïve or did not achieve a virologic response with prior treatment with pegylated interferon/ribavirin (pegIFN/RBV). Previous exposure to HCV direct-acting antivirals was prohibited. Treatment-naïve subjects were randomized in a 1:1 ratio to receive one ombitasvir 25 mg tablet, three paritaprevir 50 mg tablets and one ritonavir 100 mg capsule once-daily with food with or without ribavirin for 12 weeks. PegIFN/RBV treatment-experienced subjects received one ombitasvir 25 mg tablet, three paritaprevir 50 mg tablets and one ritonavir 100 mg capsule once-daily with food in combination with ribavirin for 12 weeks. The ribavirin dosage was 1000 mg per day for subjects weighing less than 75 kg or 1200 mg per day for subjects weighing greater than or equal to 75 kg. The primary endpoint 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.

HCV GT4-infected subjects had a median age of 51 years (range: 19 to 70); 64% were treatment-naïve, 17% were prior pegIFN/RBV null responders; 7% were prior pegIFN/RBV partial responders, 13% were prior pegIFN/RBV relapsers; 65% were male; 9% were Black; 14% had a body mass index at least 30 kg/m^2; 70% had baseline HCV RNA levels at least 800,000 IU/mL; 79% had IL28B (rs12979860) non-CC genotype; 7% had bridging fibrosis (F3).

Table 7 presents the SVR12 rates.

Table 7. SVR12 for HCV Genotype 4-Infected Subjects without Cirrhosis

Treatment outcome	Ombitasvir + Paritaprevir + Ritonavir with RBV for 12 weeks		Ombitasvir + Paritaprevir + Ritonavir for 12 weeks
	Treatment-naïve	Treatment-experienced	Treatment-naïve
	% (n/N)	% (n/N)	% (n/N)
Overall SVR12	100 % (42/42)	100% (49/49)	91% (40/44)
Outcome for subjects without SVR12			

On-treatment VF[a]	0% (0/42)	0% (0/49)	2% (1/44)
Relapse[b]	0% (0/42)	0% (0/49)	5% (2/42)
Other[c]	0% (0/42)	0% (0/49)	2% (1/44)

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

Among 131 HCV GT4 infected subjects in PEARL-I who achieved SVR12, virologic response data at post-treatment week 24 were available from 129 subjects, and 129/129 (100%) subjects maintained their response through 24 weeks post-treatment (SVR24).

16 HOW SUPPLIED/STORAGE AND HANDLING

TECHNIVIE is dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs.

Each child resistant daily dose pack contains two TECHNIVIE tablets. The NDC number is NDC-0074-3082-28.

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

Store at or below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients to review the Medication Guide for ribavirin *[see Warnings and Precautions (5.3)]*.

Risk of ALT Elevations or Hepatic Decompensation and Failure

Inform patients to watch for early warning signs of liver inflammation or failure, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice, onset of confusion, abdominal swelling, and discolored feces, and to consult their health care professional without delay if such symptoms occur *[see Warnings and Precautions (5.1 and 5.2) and Adverse Reactions (6.1)]*.

Pregnancy

Advise patients to avoid pregnancy during treatment with TECHNIVIE with ribavirin.Inform patients to notify their health care provider immediately in the event of a pregnancy *[see Use in Specific Populations (8.1)]*.

Drug Interactions

Inform patients that TECHNIVIE may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products *[see Contraindications (4), Warnings and Precautions (5.4) and Drug Interactions (7)]*.

Inform patients that contraceptives containing ethinyl estradiol are contraindicated with TECHNIVIE *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

Hepatitis C Virus Transmission

Inform patients that the effect of treatment of hepatitis C virus infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus during treatment should be taken.

Missed Dose

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

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

Instruct patients not to take more than their prescribed dose of TECHNIVIE to make up for a missed dose.

TECHNIVIE is manufactured by AbbVie Inc., North Chicago, IL 60064.

03-B283

MEDICATION GUIDE

TECHNIVIE (TEK-ni-vee)
(ombitasvir, paritaprevir and ritonavir tablets)

Important information: TECHNIVIE is taken in combination with ribavirin. You should also read the Medication Guide that comes with ribavirin.

What is the most important information I should know about TECHNIVIE?
TECHNIVIE may cause severe liver problems, especially in people with certain types of cirrhosis. These severe liver problems can lead to the need for a liver transplant, or can lead to death.
TECHNIVIE can cause increases in your liver function blood test results, especially if you use ethinyl estradiol-containing medicines (such as some birth control products).

- You must stop using ethinyl estradiol-containing medicines before you start treatment with TECHNIVIE. See the section **"Who should not take TECHNIVIE?"** for a list of these medicines.
- If you use these medicines as a method of birth control, you must use another method of birth control during treatment with TECHNIVIE, and for about **2** weeks after you finish treatment with TECHNIVIE. Your healthcare provider will tell you when you may begin taking ethinyl estradiol-containing medicines.
- Your healthcare provider should do blood tests to check your liver function during the first 4 weeks and then as needed, during treatment with TECHNIVIE.
- Your healthcare provider may tell you to stop taking TECHNIVIE if you develop signs or symptoms of liver problems.
- Tell your healthcare provider right away if you develop any of the following symptoms, or if they worsen during treatment with TECHNIVIE:
  - tiredness
  - weakness
  - loss of appetite
  - nausea and vomiting
  - yellowing of your skin or eyes
  - color changes in your stools
  - confusion
  - swelling of the stomach area

What is TECHNIVIE?

- TECHNIVIE is a prescription medicine used with ribavirin to treat people with genotype 4 chronic (lasting a long time) hepatitis C virus (HCV) infection without cirrhosis. You should also read the Medication Guide for ribavirin.
- TECHNIVIE is not for people with certain types of liver problems.
- Each TECHNIVIE tablet contains the medicines ombitasvir, paritaprevir and ritonavir.

It is not known if TECHNIVIE is safe and effective in children under 18 years of age.

Who should not take TECHNIVIE?
Do not take TECHNIVIE if you:

- **have severe liver problems**
- **take any of the following medicines:**
  - alfuzosin hydrochloride (Uroxatral®)
  - carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)
  - colchicine (Colcrys®)
  - efavirenz (Atripla®, Sustiva®)
  - ergot containing medicines including:
    - ergotamine tartrate (Cafergot®, Ergomar®, Ergostat®, Medihaler®, Migergot®, Wigraine®, Wigrettes®)
    - dihydroergotamine mesylate (D.H.E. 45®, Migranal®)
    - methylergonovine (Ergotrate®, Methergine®)
  - ethinyl estradiol-containing medicines:
    - combination birth control pills or patches, such as Lo Loestrin® FE, Norinyl®, Ortho Tri-Cyclen Lo®, Ortho Evra®

- hormonal vaginal rings such as NuvaRing®
- the hormone replacement therapy medicine, Fem HRT®

- lovastatin (Advicor®, Altoprev®, Mevacor®)
- midazolam, when taken by mouth
- phenytoin, (Dilantin®, Phenytek®)
- phenobarbital (Luminal®)
- pimozide (Orap®)
- rifampin (Rifadin®, Rifamate®, Rifater® Rimactane®)
- sildenafil citrate (Revatio®), when taken for pulmonary artery hypertension (PAH)
- simvastatin (Simcor®, Vytorin®, Zocor®)
- St. John's wort (Hypericum perforatum) or a product that contains St. John's wort
- triazolam (Halcion®)

- **have had a severe skin rash after taking ritonavir (Norvir®)**

Before taking TECHNIVIE tell your healthcare provider about all your medical conditions, including if you:

- have liver problems other than hepatitis C infection. **See "Who should not take TECHNIVIE?"**

- have HIV infection

- have had a liver transplant. If you take the medicines tacrolimus (Prograf®) or cyclosporine (Gengraf®, Neoral®, Sandimmune®) to help prevent rejection of your transplanted liver, the amount of these medicines in your blood may increase during treatment with TECHNIVIE.
  - Your healthcare provider should check the level of tacrolimus or cyclosporine in your blood, and if needed may change your dose of these medicines or how often you take them.
  - When you finish taking TECHNIVIE or if you have to stop TECHNIVIE for any reason, your healthcare provider should tell you what dose of tacrolimus or cyclosporine to take and how often you should take it.

- are pregnant or plan to become pregnant. It is not known if TECHNIVIE will harm your unborn baby. **When taking TECHNIVIE in combination with ribavirin you should also read the ribavirin Medication Guide for important pregnancy information.**

- are breastfeeding or plan to breastfeed. It is not known if TECHNIVIE passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take TECHNIVIE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with TECHNIVIE. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with TECHNIVIE.

- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take TECHNIVIE with other medicines.

- When you finish treatment with TECHNIVIE:
  - If your healthcare provider changed the dose of one of your usual medicines during treatment with TECHNIVIE: Ask your healthcare provider about when you should change back to your original dose after you finish treatment with TECHNIVIE.
  - If your healthcare provider told you to stop taking one of your usual medicines during treatment with TECHNIVIE: Ask your healthcare provider if you should start taking these medicines again after you finished treatment with TECHNIVIE.

How should I take TECHNIVIE?

- Take TECHNIVIE exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.

- Do not stop taking TECHNIVIE without first talking with your healthcare provider.
- Take 2 TECHNIVIE tablets every day in the morning, with a meal.
- If you take too much TECHNIVIE, call your healthcare provider or go to the nearest emergency room right away.
- TECHNIVIE is supplied in **monthly cartons that contain enough medicine for 28 days**.
  - Each monthly carton of TECHNIVIE contains **4 smaller cartons**.
  - Each of the 4 smaller cartons contains enough child resistant **daily dose packs** of medicine to last for **7 days (1 week)**.
  - Each **daily dose pack** contains all of your TECHNIVIE medicine for **1 day** (2 tablets).
  - Follow the instructions on each daily dose pack about how to remove the tablets.
- If you miss a dose of TECHNIVIE tablets, and it is **less than 12 hours** from the time you usually take your dose, **take the missed dose** with a meal as soon as possible. Then take your next dose at your usual time with a meal.
- If you miss a dose of TECHNIVIE tablets, and it is **more than 12 hours** from the time you usually take your dose, **skip the missed dose**. Then take your next dose at your usual time with a meal.
- Do not take more than your prescribed dose of TECHNIVIE to make up for a missed dose.

What are the possible side effects of TECHNIVIE?

TECHNIVIE can cause serious side effects. See **"What is the most important information I should know about TECHNIVIE?"**

Common side effects of TECHNIVIE when used with ribavirin include:

- feeling weak
- tiredness
- nausea
- sleep problems

These are not all the possible side effects of TECHNIVIE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TECHNIVIE?

- Store TECHNIVIE at or below 86°F (30°C).

Keep TECHNIVIE and all medicines out of the reach of children.

General information about the safe and effective use of TECHNIVIE

It is not known if treatment with TECHNIVIE will prevent you from infecting another person with the hepatitis C virus during your treatment. Talk with your healthcare provider about ways to prevent spreading the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TECHNIVIE for a condition for which it was not prescribed. Do not give TECHNIVIE to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TECHNIVIE that is written for health professionals.

What are the ingredients in TECHNIVIE?

Active ingredients: ombitasvir, paritaprevir, and ritonavir

Inactive ingredients: copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and red iron oxide.

Manufactured by AbbVie Inc., North Chicago, IL 60064.

www.technivie.com or call 1-844-283-2464.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Issued: January 2016
03-B283

NDC 0074–3082–28

Rx only

technivie™

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

Each tablet contains ombitasvir, paritaprevir, ritonavir 12.5 mg/ 75 mg/ 50 mg

Do not use if seal on top of carton is broken or missing

Keep out of reach of children

Each carton contains 14 tablets in 7 wallets for 1 week of treatment

Each wallet contains 2 tablets

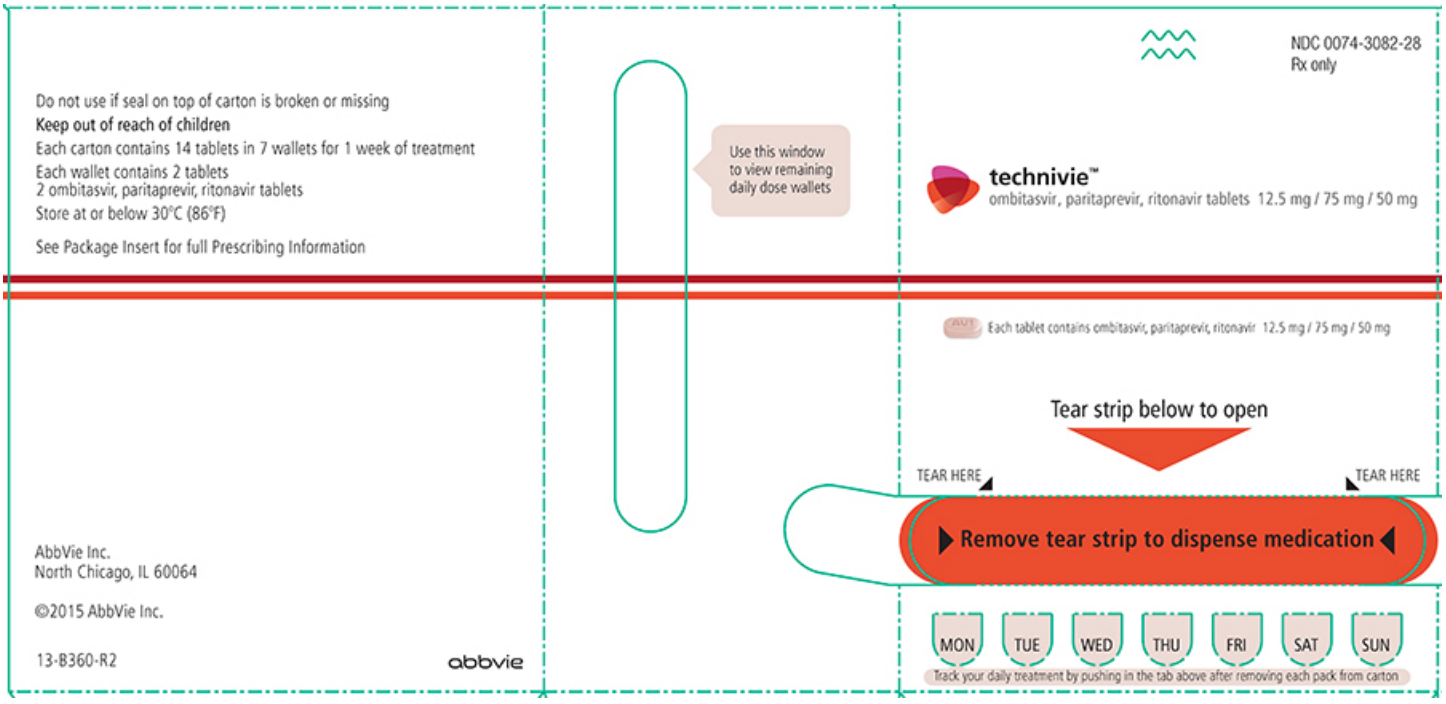
2 ombitasvir, paritaprevir, ritonavir tablets

Store at or below 30°C (86°F)

See Package Insert for full Prescribing Information

AbbVie Inc.

North Chicago, IL 60064



TECHNIVIE

ombitasvir and paritaprevir and ritonavir kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0074-3082

Packaging

#	Item Code	Package Description	Multilevel Packaging
1	NDC:0074-3082-28	4 CARTON in 1 CARTON	contains a CARTON
1		7 DOSE PACK in 1 CARTON	This package is contained within the CARTON (0074-3082-28) and contains a DOSE PACK
1		1 KIT in 1 DOSE PACK	This package is contained within a CARTON and a CARTON (0074-3082-28)

QUANTITY OF PARTS

Part #	Package Quantity	Total Product Quantity
Part 1		2

Part 1 of 1

TECHNIVIE

ombitasvir and paritaprevir and ritonavir tablet, film coated

Product Information

Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RITONAVIR (RITONAVIR)	RITONAVIR	50 mg
OMBITASVIR HEMINONAHYDRATE (OMBITASVIR)	OMBITASVIR	12.5 mg
PARITAPREVIR DIHYDRATE (PARITAPREVIR)	PARITAPREVIR	75 mg

Inactive Ingredients

Ingredient Name	Strength
COPOVIDONE K25-31	
SILICON DIOXIDE	
POLYVINYL ALCOHOL	
TALC	
FERRIC OXIDE RED	
SODIUM STEARYL FUMARATE	
TITANIUM DIOXIDE	
POLYETHYLENE GLYCOL 3350	
SORBITAN MONOLAURATE	
TOCOPHERSOLAN	
PROPYLENE GLYCOL LAURATES	

Product Characteristics

Color	PINK	**Score**	no score
Shape	OVAL ((OBLONG BICONVEX))	**Size**	19mm
Flavor		**Imprint Code**	AV1
Contains			

Packaging

#	Item Code	Package Description	Multilevel Packaging

Package Information Not Applicable

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207931		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207931	07/24/2015	

Labeler - AbbVie Inc. (078458370)

Revised: 02/2016 AbbVie Inc.