



Ombitasvir/Paritaprevir/Ritonavir (Technivie™) Abbreviated New Drug Update

August 2015

OVERVIEW¹

- 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 to pharmacologically boost paritaprevir), from AbbVie, approved for:
 - The treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis, in combination with ribavirin.
 - Technivie is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B).
- Contraindications/Warnings
 - Patients with severe hepatic impairment (Child-Pugh C).
 - Co-administration with drugs that are highly dependent on CYP3A for clearance.
 - Co-administration with drugs that are moderate and strong inducers of CYP3A.
 - Patients with a known hypersensitivity to ritonavir (e.g., toxic epidermal necrosis, Stevens-Johnson syndrome).
 - 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 four weeks of treatment. For ALT elevations on Technivie, monitor closely and follow recommendations in full prescribing information.
 - Risks Associated With Ribavirin Combination Treatment: The warnings and precautions for ribavirin also apply to this combination regimen.
 - 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.
 - The contraindications to ribavirin also apply to this combination regimen, including
 - ❖ Women who are pregnant;
 - ❖ Men whose female partners are pregnant;
 - ❖ Patients with known hypersensitivity reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme);
 - ❖ Patients with autoimmune hepatitis;
 - ❖ Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia); and
 - ❖ Patients with creatinine clearance less than 50 ml/min.

- Availability
 - ❑ Fixed dose tablet: 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir
- Dosage and Administration
 - ❑ The recommended dosage of Technivie is 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 weight-based ribavirin (1,000 mg per day for patients < 75 kg and 1,200 mg per day for those ≥ 75 kg, divided and administered twice daily with food).
- Adverse Events (≥ 10%)
 - ❑ Asthenia, fatigue, nausea, and insomnia
- Drug Interactions

Drug Class	Drug(s) Within the Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	alfuzosin HCl	Potential for hypotension.
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.
Herbal Product	St. John's Wort (<i>Hypericum perforatum</i>)	Ombitasvir, paritaprevir, and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of Technivie.
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	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	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. Co-administration of triazolam or orally-administered midazolam with Technivie may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

Drug Interactions (continued)

Concomitant Drug Class: Drug Name	Effect On Concentration	Clinical Comments
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	The maximum daily dose of ketoconazole should be limited to 200 mg per day when co-administered with Technivie.
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	<u>Patients already receiving quetiapine initiating Technivie:</u> Consider alternative anti-HCV therapy to avoid increases in quetiapine exposures. If co-administration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. <u>Patients already receiving Technivie initiating quetiapine:</u> Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Calcium Channel Blockers		
amlodipine	↑ amlodipine	Consider dose reduction for amlodipine. Clinical monitoring is recommended.
Corticosteroids (Inhaled/Nasal)		
fluticasone	↑ fluticasone	Serum cortisol concentrations may be reduced; alternative corticosteroids should be considered, particularly for long-term use.
Diuretics		
furosemide	↑ furosemide (C _{max})	Clinical monitoring recommended; therapy should be individualized based on patient response.

Drug Interactions (continued)

Concomitant Drug Class: Drug Name	Effect On Concentration	Clinical Comments
HIV-Antivirals		
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 800mg (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 prolongation associated with higher concentrations of rilpivirine.
HMG CoA Reductase Inhibitors		
pravastatin	↑pravastatin	Dose of pravastatin should not exceed 40 mg/day
Immunosuppressants		
cyclosporine	↑cyclosporine	Reduce cyclosporine dose to 1/5 of the current dose when Technivie is initiated; subsequent dose modifications should be based on cyclosporine blood concentration measurements. Upon completion of Technivie, resumption of cyclosporine should be guided by cyclosporine blood concentrations; frequent assessment of renal function and cyclosporine-related side effects is recommended.
tacrolimus	↑tacrolimus	Do not administer tacrolimus on the day Technivie is initiated. Beginning the day after Technivie is initiated, tacrolimus should be restarted at a reduced dose based on tacrolimus blood concentrations; typical tacrolimus dosing is 0.5 mg every 7 days. Tacrolimus blood concentrations should guide subsequent dose and frequency modifications. Upon completion of Technivie, the appropriate time to resume original tacrolimus dose should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus related side effects is recommended.

Drug Interactions (continued)

Concomitant Drug Class: Drug Name	Effect On Concentration	Clinical Comments
Long-Acting Beta-Agonists		
salmeterol	↑salmeterol	Concurrent administration of Technivie and salmeterol is not recommended due to risk of cardiovascular adverse effects related to salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Narcotic Analgesics		
buprenorphine/naloxone	↑buprenorphine ↑norbuprenorphine	No dosage adjustment is required; however, patients should be closely monitored for sedation and cognitive effects.
Proton Pump Inhibitors		
omeprazole	↓omeprazole	Monitor for decreased efficacy of omeprazole; consider increasing omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg/day of omeprazole.
Sedatives/Hypnotics		
alprazolam	↑alprazolam	Clinical monitoring is recommended; consider dose decrease of alprazolam based on patient's clinical response.

- Pregnancy
 - 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, paritaprevir, or ritonavir at exposures higher than the recommended clinical dose.
 - When administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant.
- Clinical Trials
 - The efficacy and safety of Technivie was evaluated in a single clinical trial in patients with genotype 4 chronic HCV. PEARL-I was a randomized, global, multicenter, open-label trial that enrolled 135 adults with HCV genotype 4 infection without cirrhosis who were either treatment-naïve or did not achieve a virologic response with prior treatment with pegylated interferon + ribavirin (PEG/RBV). Previous exposure to HCV direct-acting antivirals was prohibited. Treatment-naïve patients 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 in combination with ribavirin (n=42) or without ribavirin (n=44) for 12 weeks. PEG/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 (49 patients). The ribavirin dosage was 1,000 mg per day for patients weighing less than 75 kg or 1,200 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. All 42 of the treatment-naïve patients taking ombitasvir +

paritaprevir + ritonavir with ribavirin for 12 weeks achieved an SVR12 (100%). All 49 of the treatment-experienced patients taking ombitasvir + paritaprevir + ritonavir with ribavirin for 12 weeks achieved an SVR12 (100%). Out of the 44 treatment-naïve patients taking ombitasvir + paritaprevir + ritonavir without ribavirin, 40 patients achieved an SVR12 (91%). Of the 129 patients that achieved an SVR12, all 129 maintained their response 24 weeks after the end of treatment (SVR24).

CLINICAL CONSIDERATIONS

- Technivie is only approved for the treatment of HCV genotype 4 and should not be used in patients with other genotypes. It is not approved in cirrhotic patients with HCV genotype 4.
- Based on the AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C, Technivie in combination with weight-based ribavirin for 12 weeks is a recommended regimen for the treatment of HCV genotype 4 in treatment-naïve and treatment experienced patients.²

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Hepatitis C Agents
Clinical Edit	Refer to the Magellan Rx Management clinical criteria
Quantity Limit	Maximum quantity of 1 ombitasvir/paritaprevir/ritonavir pack per 28 days
Duration of Approval	Refer to the Magellan Rx Management clinical criteria
Drug to Disease Hard Edit	Pediatrics, Age < 18 years

REFERENCES

1 Technivie [package insert]. North Chicago, IL; AbbVie; July 2015.

2HCV Guidance: AASLD/IDSA/IAS-USA. Recommendations for testing, managing, and treating hepatitis C. Available at: <http://www.hcvguidelines.org/full-report>. Accessed on August 19, 2015.