

# Ombitasvir, paritaprevir/ritonavir (Technivie<sup>®</sup>)

## National Abbreviated Review Drug Monograph

December 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel,  
VISN Pharmacist Executives and Office of Public Health

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

### FDA Approval Information<sup>1</sup>

<b>Description/ Mechanism of Action</b>	Technivie is a fixed-dose combination of ombitasvir, paritaprevir, and ritonavir. Ritonavir does not have activity against Hepatitis C virus (HCV); it is included in the regimen as a pharmacokinetic enhancer (i.e. increase concentration of paritaprevir). The other two agents are direct-acting antivirals with different mechanisms of action. Ombitasvir is a NS5A inhibitor and paritaprevir is a NS3/4A protease inhibitor.
<b>Indication(s) under Review in this document</b>	Fixed-dose combination of ombitasvir, paritaprevir and ritonavir with ribavirin is indicated for the treatment of chronic hepatitis C genotype 4 infections in adults <i>without</i> cirrhosis.  NOTE: Per prescribing information, this combination may be administered without ribavirin in treatment-naïve patients who cannot tolerate ribavirin
<b>Dosage Form(s) Under Review</b>	Ombitasvir, paritaprevir, ritonavir 12.5/75/50mg tablet
<b>REMS</b>	NO REMS
<b>Pregnancy Rating</b>	Pregnancy Category B; however, when ribavirin is co-administered, then regimen is contraindicated in pregnant women and in men whose female partners are pregnant.

### Executive Summary<sup>1-2</sup>

<b>Efficacy</b>	The FDA approval of ombitasvir, paritaprevir and ritonavir with ribavirin was primarily based on one phase 2b randomized, open-label, multi-center trial (called PEARL-1). The PEARL-1 clinical trial evaluated HCV genotype 4 patients without cirrhosis for treatment durations of 12 weeks. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment. SVR was achieved 100% (42/42) treatment-naïve and 100% (49/49) treatment-experienced patients that received ombitasvir, paritaprevir and ritonavir with ribavirin.
<b>Safety</b>	Safety data are primarily from PEARL-1. Most common adverse reactions (≥10%) were asthenia, fatigue, nausea, and insomnia. Laboratory abnormalities included elevations in bilirubin elevations and decreases in hemoglobin.
<b>Potential Impact</b>	Fixed-dose combination of ombitasvir, paritaprevir and ritonavir administered with ribavirin is indicated for patients with chronic HCV Genotype 4 without cirrhosis. Ombitasvir, paritaprevir and ritonavir is administered once daily with for 12 weeks.

### Background

<b>Purpose for review</b>	Recent FDA approval: July 2015
	<b>Issues to be determined:</b> <ul style="list-style-type: none"><li>✓ Evidence of need</li><li>✓ Does ombitasvir, paritaprevir, and ritonavir offer advantages over current VANF agents?</li><li>✓ What safety issues need to be considered?</li></ul>

<b>Other therapeutic options</b>	<b>Formulary Alternatives with FDA approval for HCV Genotype 4 Patients</b>	<b>Other Considerations</b>
	Ledipasvir/sofosbuvir (LDV/SOF)	Fixed-dose combination product: One tablet once daily without ribavirin for 12

**Efficacy (FDA Approved Indications)<sup>1-2</sup>****Literature Search Summary**

A literature search was performed on PubMed/Medline (1966 to November 2015) using the search terms ombitasvir, paritaprevir and ritonavir and Technivie. The search was limited to studies performed in humans and published in the English language. The pivotal phase 3 clinical trial published in peer-reviewed journals was included.

**Review of Efficacy**

The FDA approval of ombitasvir, paritaprevir and ritonavir with ribavirin was primarily based on one phase 2b randomized, open-label, multi-center trial (called PEARL-1, Refer to Table 1).<sup>1</sup> The PEARL-1 clinical trial evaluated HCV genotype 4 patients without cirrhosis for treatment duration of 12 weeks. Population included treatment-naïve or treatment-experienced with PEG/riba. The former were randomized to receive therapy with or without ribavirin while all treatment-experienced patients received ribavirin. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment. Key exclusion criteria were co-infection with HIV and/or hepatitis B as well as solid organ recipient. Demographic included median age 51 years, 65% male, 64% treatment-naïve, 70% with baseline HCV RNA levels at least 800,000 IU/mL and 7% with bridging fibrosis (F3).

**Table 1. SVR12 reported in Phase 2b Clinical Trial<sup>a</sup>**

SVR12	Technivie with RBV		Technivie without RBV
	Treatment-naïve	Treatment-experienced	Treatment-naïve
	100% (42/42)	100% (49/49)	91% (40/44) <sup>b</sup>

<sup>a</sup>Data reported according to prescribing information<sup>1</sup>

<sup>b</sup>In patients that did not achieve SVR, outcomes included virologic failure (n=1); relapse (n=2) and lost to follow-up (n=1)  
Overall Quality of Evidence: Moderate (Refer to Appendix A; pivotal clinical trial sponsored by Abbvie)

**Potential Off-Label Use**

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's [Guidance on "Off-label" Prescribing](#) (available on the VA PBM intranet site only).

- Patients with HCV Genotype 4 co-infected with HIV

**Safety** (for more detailed information refer to the product package insert)<sup>1</sup>

	Comments
<b>Boxed Warning</b>	<ul style="list-style-type: none"> <li>• None</li> </ul>
<b>Contraindications</b>	<ul style="list-style-type: none"> <li>• If co-administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen.</li> <li>• Patients with moderate to severe hepatic impairment.</li> <li>• Co-administration with drugs that are highly dependent on CYP3A for clearance; moderate and strong inducers of CYP3A</li> <li>• Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome).</li> </ul>
<b>Warnings/Precautions</b>	<ul style="list-style-type: none"> <li>• Hepatic Decompensation and Hepatic Failure in Patients 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.</li> <li>• ALT Elevations: discontinue ethinyl estradiol-containing medications prior to starting ombitasvir, paritaprevir and ritonavir (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations, monitor closely and follow recommendations in full prescribing information.</li> <li>• If co-administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen.</li> <li>• Co-administration of certain other drugs may result in known or potentially significant drug interactions.</li> </ul>

- Risk of HIV protease inhibitor drug resistance in HCV/HIV co-infected patients: Ritonavir is also an HIV protease inhibitor and can select for HIV protease inhibitor resistance-associated substitutions. HCV/HIV co-infected patients treated with ombitasvir, paritaprevir and ritonavir should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV protease inhibitor drug resistance.

### Safety Considerations

The safety assessment was primarily based HCV infected genotype 4 patients without cirrhosis who received ombitasvir, paritaprevir and ritonavir with or without ribavirin (i.e., PEARL-1).

### Adverse Reactions

Common adverse reactions	<ul style="list-style-type: none"> <li>• Most common adverse reactions (<math>\geq 10\%</math>) were asthenia, fatigue, nausea, and insomnia.</li> </ul>
Death/Serious adverse reactions	<ul style="list-style-type: none"> <li>• The prescribing did not address deaths during PEARL-1. It did state that no patients receiving ombitasvir, paritaprevir and ritonavir with ribavirin experienced serious adverse reaction.</li> </ul>
Discontinuations due to adverse reactions	<ul style="list-style-type: none"> <li>• None.</li> </ul>
Laboratory Abnormalities	<p><b>ALT elevations:</b> No patients experienced ALT levels <math>&gt;5X</math> ULN after starting treatment.</p> <p><b>Bilirubin elevations:</b> 5% (7/134) of patients experienced bilirubin levels at least 2X ULN after starting treatment. Of note, all were receiving ribavirin. These bilirubin increases were predominately indirect and related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced hemolysis. Bilirubin elevations typically peaked by Week 1 and generally resolved with ongoing therapy. Bilirubin elevations were not associated with serum ALT elevations.</p> <p><b>Anemia/Decreased Hemoglobin:</b> Mean change from baseline in hemoglobin levels in patients treated with ribavirin were -2.1 g/dL compared to -0.4g/dL in patients that did not receive ribavirin.</p>

### Drug-Drug Interactions<sup>1</sup>

- Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes and co-administration with strong CYP3A inhibitors may increase concentrations of paritaprevir and ritonavir. In contrast, ombitasvir is primarily metabolized via amide hydrolysis. Ombitasvir, paritaprevir, and ritonavir are substrates of P-gp. Ombitasvir, paritaprevir and ritonavir are substrates of BCRP. Paritaprevir is a substrate of BCRP, OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may increase the plasma concentrations of such drugs.
- Consult the prescribing information including contra-indication and precautions/warnings prior to use for potential drug interactions and on-going evaluation.

### Risk Evaluation

As of November 2015	Comments										
Sentinel event advisories	<ul style="list-style-type: none"> <li>• Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis</li> </ul>										
Look-alike/sound-alike error potentials	<ul style="list-style-type: none"> <li>• Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List):</li> </ul> <table border="1" data-bbox="522 1646 1393 1709"> <thead> <tr> <th>NME Drug Name</th> <th>Lexi-Comp</th> <th>First DataBank</th> <th>ISMP</th> <th>Clinical Judgment</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment					
NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment							

	Ombitasvir, Paritaprevir, Ritonavir 12.5/75/50mg tab	None	None	None	Ombitasvir, paritaprevir, and ritonavir fixed-comb'n tab + dasabuvir (Viekira Pak)  If fixed dose comb'n ingredients listed first alphabetically, ombitasvir has LASA potential with oseltamivir
	Technivie	None	None	None	Tekturna Technetium

### Other Considerations

- None

### Dosing and Administration<sup>1</sup>

Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg co-formulated tablets once daily (in the morning) with a meal without regard to fat or calorie content. Co-administration with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day) is recommended.

Population includes HCV monoinfected or HCV/HIV-1 co-infected stabilized on certain antiretroviral regimens	Dosage Regimens	Total treatment duration
Genotype 4 without cirrhosis <sup>a</sup>	Technivie plus ribavirin <sup>b</sup>	12 weeks

<sup>a</sup>Population: treatment-naïve and treatment-experienced patients with peginterferon/ribavirin.

<sup>b</sup>Technivie administered without ribavirin for 12 weeks may be considered for treatment-naïve patients who cannot tolerate ribavirin

### Special Populations (Adults)<sup>1</sup>

	Comments
<b>Elderly</b>	<ul style="list-style-type: none"> <li>No dosage adjustments are recommended in elderly.</li> </ul>
<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>Pregnancy Category B: Adequate and well controlled studies have not been conducted in pregnant women; this regimen should be used during pregnancy only if clearly needed.</li> <li>If co-administered with ritonavir, 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 in pregnancy.</li> </ul>
<b>Lactation</b>	<ul style="list-style-type: none"> <li>It is not known whether any of the components or their metabolites are present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for this regimen and any potential adverse effects on the breastfed child.</li> <li>If administered with ribavirin, the nursing mothers information for ribavirin applies to this combination regimen (see prescribing information for ribavirin).</li> </ul>
<b>Renal Impairment</b>	<ul style="list-style-type: none"> <li>No dosage adjustment of ombitasvir, paritaprevir and ritonavir is required in patients with mild, moderate or severe renal impairment. It has not been studied in patients on dialysis. However, ribavirin is known to be substantially excreted by the kidney, and the risks of adverse reactions are greater in patients with impaired renal function. The total daily dose of ribavirin should be reduced for patients with creatinine clearance less than or equal to 50 mL/min as follows: creatinine clearance between 30-50ml/min use alternating doses of 200mg and 400mg every other day; for creatinine clearance &lt;30ml/min or for hemodialysis use 200mg daily.</li> </ul>

<b>Hepatic Impairment</b>	<ul style="list-style-type: none"> <li>No dosage adjustment in patients with mild hepatic impairment (Child-Pugh A). It is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) and hepatic impairment (Child-Pugh C).</li> </ul>
<b>Pharmacogenetics/genomics</b>	<ul style="list-style-type: none"> <li>No data identified in prescribing information.</li> </ul>
<b>HIV co-infected patients</b>	<ul style="list-style-type: none"> <li>Ritonavir is also an HIV protease inhibitor and can select for HIV protease inhibitor resistance-associated substitutions. According to prescribing information, any HCV/HIV co-infected patients treated with ombitasvir, paritaprevir and ritonavir regimen should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV protease inhibitor drug resistance. However, potential antiretroviral regimens that can be co-administered with the ombitasvir, paritaprevir and ritonavir need to be carefully evaluated prior to initiation of the HCV regimen. Refer to <a href="http://www.hep-druginteractions.org">http://www.hep-druginteractions.org</a> for potential options.</li> </ul>

### Projected Place in Therapy

- The VHA HCV Registry Reports indicates that there are 1219 Veterans with HCV GT4 (264 with Fib4>3.25) as of December 2014.<sup>3</sup>
- The FDA approval of ombitasvir, paritaprevir and ritonavir with ribavirin was primarily based on one phase 2b randomized, open-label, multi-center trial (called PEARL-1). The PEARL-1 clinical trial evaluated HCV genotype 4 patients without cirrhosis for treatment durations of 12 weeks. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment. SVR was achieved 100% (42/42) treatment-naïve and 100% (49/49) treatment-experienced patients that received ombitasvir, paritaprevir and ritonavir with ribavirin.
- Safety data are primarily from PEARL-1. Most common adverse reactions with ribavirin ( $\geq 10\%$ ) were asthenia, fatigue, nausea, and insomnia. Laboratory abnormalities included elevations in bilirubin elevations and decreases in hemoglobin. Ombitasvir, paritaprevir and ritonavir regimen has significant drug-interactions; therefore, patient should be assessed for potential drug-interactions at baseline and throughout therapy.
- Fixed-dose combination of ombitasvir, paritaprevir and ritonavir administered with ribavirin is indicated for patients with chronic HCV Genotype 4 without cirrhosis. Ombitasvir, paritaprevir and ritonavir is administered once daily with for 12 weeks.

**References**

1. Technivie [package insert]. AbbVie, Inc., North Chicago, IL; October 2015.
2. Hézode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naïve and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-D): a randomised, open-label trial. *Lancet* 2015; 385: 2502–09.
3. Office of Public Health Hepatitis C Infection Status of Hepatitis C Registry Patients 2014 (internal data).

---

**Prepared: Melinda Neuhauser, PharmD, MPH and Pam Belperio, PharmD, December 2015**

**Contact person: Melinda Neuhauser, PharmD, MPH, PBM Services**

---

## **Appendix A: GRADEing the Evidence**

### Designations of Quality

#### Quality of evidence designation

#### Description

High

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).

Moderate

Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.

Low

Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-19.