Ombitasvir, paritaprevir/ritonavir plus dasabuvir (Viekira Pak®)

National Drug Monograph

January 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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[1]

Description/ Mechanism of Action	Viekira Pak contains ombitasvir, paritaprevir, and ritonavir as a fixed-dose combination that is co-packaged with dasabuvir. 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 three agents are direct-acting antiretrovirals with different mechanisms of action. Ombitasvir is a NS5A inhibitor; paritaprevir is a NS3/4A protease inhibitor, and dasabuvir a non-nucleotide NS5B polymerase inhibitor.
Indication(s) under Review in this document	Ombitasvir, paritaprevir/ritonavir plus dasabuvir with or without ribavirin is indicated for the treatment of chronic hepatitis C genotype 1 infection in adults including those with compensated cirrhosis.
Dosage Form(s) Under Review	Ombitasvir, paritaprevir, ritonavir 12.5/75/50mg tablet and dasabuvir 250mg tablet
REMS	NO REMS
Pregnancy Rating	Pregnancy Category B

Executive Summary[1]

Efficacy	• The FDA approval of ombitasvir, paritaprevir/ritonavir plus dasabuvir with or without ribavirin was primarily based on six Phase 3 randomized, multi-center trials (Refer to Table 1).[1] These clinical trials evaluated HCV genotype 1 patients with compensated liver disease with and without cirrhosis for treatment durations of 12 or 24 weeks. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment. The FDA approved regimens for ombitasvir, paritaprevir/ritonavir plus dasabuvir with or without ribavirin with or without ribavirin achieved SVRs in the range of 95-100%. • In addition, ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin were evaluated in HCV genotype patients with liver transplant and patients co-infected with HIV. Please note the potential for significant drug-drug interactions.
Safety	• Pooled safety data are available from six Phase 3 clinical trials. In patients without co-administration of ribavirin, the most common adverse reactions (≥5%) were nausea, pruritus and insomnia. In patients with co-administered ribavirin, most common adverse reactions (≥10%) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. Laboratory abnormalities included ALT and bilirubin elevations.
Potential Impact	• Ombitasvir, paritaprevir/ritonavir plus dasabuvir with or without ribavirin is an FDA approved interferon-free regimen for patients with chronic HCV Genotype 1. It is available as a fixed-dose combination of ombitasvir, paritaprevir, and ritonavir that is co-packaged with dasabuvir. Ombitasvir, paritaprevir/ritonavir is administered once daily while dasabuvir is administered twice daily with or without ribavirin for 12 or 24 weeks depending on patient characteristics.

Background

Purpose for review	The purpose of the review is to evaluate the efficacy and safety of ombitasvir, paritaprevir/ritonavir plus dasabuvir. Dosage and Administration: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50

mg co-formulated tablets once daily (in the morning) **and** one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal. For certain patient populations, co-administration with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day) is recommended. Refer to Dosage and Administration Section for more details.

Other therapeutic options

Formulary Alternatives for interferon free regimens for HCV Genotype 1 Patients	Other Considerations
Ledipasvir/sofosbuvir (LDV/SOF)	Fixed-dose combination product: One tablet once daily Minimal drug interactions Can be used in patients that experienced previous virologic failure with a NS3-4A protease inhibitor containing regimen (e.g., boceprevir, telaprevir, simeprevir) or sofosbuvir-based regimen.
Sofosbuvir plus simeprevir	2 pills once a day (i.e., not a fixed-dose combination product) Simeprevir plus sofosbuvir should not be used in patients that experienced previous virologic failure with a NS3-4A protease inhibitor containing regimen (e.g., boceprevir or telaprevir).

Efficacy (FDA Approved Indications)[1-4]

Literature Search Summary
A literature search was performed on PubMed/Medline (1966 to December 2014) using the search terms ombitasvir, paritaprevir/ritonavir with dasabuvir and Viekira. The search was limited to studies performed in humans and published in the English language. The pivotal phase 3 clinical trials published in peer-reviewed journals were included.

Review of Efficacy
The FDA approval of ombitasvir, paritaprevir/ritonavir plus dasabuvir with or without ribavirin was primarily based on six Phase 3 randomized, multi-center trials (Refer to Table 1).[1] These clinical trials evaluated HCV genotype 1 patients with compensated liver disease with and without cirrhosis for treatment durations of 12 or 24 weeks. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment. For patients that did not achieve SVR12, outcomes were also provided according to on-treatment virologic failure, post-treatment virologic relapse through post-treatment Week 12 or failure due to other non-virologic reasons (e.g., premature discontinuation, adverse event, lost to follow-up, consent withdrawn) (data are not provided; refer to prescribing information). Refer to Table 1 for SVR according to data provided in the prescribing information[1] and Table 2 for SVR according to data provided in published literature for these six trials. In addition, ombitasvir, paritaprevir/ritonavir plus dasabuvir was evaluated in HCV genotype patients with liver transplant and co-infected with HIV.

Table 1. Summary of Phase 3 Clinical Trials reported in Prescribing Information[1]

Study	Population	Regimen	SVR12
SAPPHIRE-1	Treatment-naïve HCV Genotype 1 patients without cirrhosis	Viekira Pak + RBV for 12 wks	GT1a: 96% (308/322)
SAPPHIRE-II	Treatment-experienced HCV Genotype 1 patients without cirrhosis	Viekira Pak + RBV for 12 wks	GT1a: 96% (166/173)
PEARL-II	Treatment-experienced HCV Genotype 1b patients without cirrhosis	Viekira Pak + RBV for 12wks Viekira Pak for 12 wks	Not provided GT1b: 100% (91/91)

PEARL-III	Treatment-naïve HCV Genotype 1b patients without cirrhosis	Viekira Pak + RBV for 12wks Viekira Pak for 12 wks	Not provided GT1b: 100% (209/209)
PEARL-IV	Treatment-naïve HCV Genotype 1a patients without cirrhosis	Viekira Pak + RBV for 12wks Viekira Pak for 12wks	GT1a: 97% (97/100) Not provided
TURQUOISE-II	Treatment-naïve and -experienced HCV Genotype 1 patients with cirrhosis	Viekira Pak + RBV for 12 wks Viekira Pak + RBV for 24 wks	GT1a: 89% (124/140)[a] GT1b: 99% (67/68) GT1a: 95% (115/121) [a] [a]TX Difference: 6% (95% CI 0.1 to13)

Treatment-experienced included prior relapsers, partial responders, or null responders to peg/ribavirin treatment.
RBV: ribavirin

Table 2. Summary of Phase 3 Clinical Trials reported in published literature[2-6]

Study	Population	Regimen	SVR12
SAPPHIRE-1	Treatment-naïve HCV Genotype 1 patients without cirrhosis	Viekira Pak + RBV for 12 wks	GT1: 96.2% (455/473) GT1a: 95.3% (307/322) GT1b: 98.0% (148/151)
SAPPHIRE-II	Treatment-experienced HCV Genotype 1 patients without cirrhosis	Viekira Pak + RBV for 12 wks	GT1: 96.3% (286/297) GT1a: 96.0% (166/173) GT1b: 96.7% (119/123) For GT1: Prior relapse: 95.3% (82/86) Prior partial response: 100% (65/65) Prior null response: 95.2% (139/146)
PEARL-II	Treatment-experienced HCV Genotype 1b patients without cirrhosis	Viekira Pak + RBV for 12wks Viekira Pak for 12 wks	GT1b: 96.6% (85/88) GT1b: 100% (91/91) TX Difference: 3.4% (95% CI -0.4 to 7.2)
PEARL-III	Treatment-naïve HCV Genotype 1b patients without cirrhosis	Viekira Pak + RBV for 12wks Viekira Pak for 12 wks	GT1b: 99.5% (209/210) GT1b: 99.0% (207/209) TX Difference: -0.5% (95% CI -2.1 to 1.1)
PEARL-IV	Treatment-naïve HCV Genotype 1a patients without cirrhosis	Viekira Pak + RBV for 12wks Viekira Pak for 12wks	GT1a: 97% (97/100) GT1a: 90.2% (185/205) TX Difference: -6.8% (95% CI -12 to -1.5)
TURQUOISE -II	Treatment-naïve and -experienced HCV Genotype 1 patients with cirrhosis	Viekira Pak + RBV for 12 wks Viekira Pak + RBV for 24 wks	GT1: 91.8% (191/208) GT1a: 88.6% (124/140) GT1b: 98.5% (67/68) GT1: 95.9% (165/172) GT1a: 94.2% (114/121) GT1b: 100% (51/51) TX Difference GT1 for 12 weeks vs

			24 weeks (p=0.09) Refer to Table 3 for more stratified results.

Overall Quality of Evidence: High (Refer to Appendix A; note all 6 pivotal clinical trials sponsored by Abbvie); RBV: ribavirin

SAPPHIRE-I: Treatment-naïve HCV Genotype 1 patients without cirrhosis[2]

- Double-blind, placebo-controlled trial
- Randomization in 3:1 ratio to receive ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 12 weeks or placebo for 12 weeks. Stratified by HCV genotype (1a vs non-1a) and *IL28B* genotype (CC vs non-CC).
- Following 12 weeks of double-blind part of trial, the placebo arm received ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 12 weeks (open-label).
- Demographics of the arm randomized to ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 12 weeks (n=473) included mean age 49.4 years old (range: 18 to 70); 57.3% male; 90.5% white, 5.5% black; 5.7% Hispanic; baseline HCV RNA 6.40±0.62 $\log_{10}$IU/mL; 68.1% Genotype 1a; 30.4% *IL28B* CC genotype; and 23.3% with Fibrosis score ≥ 2.

SAPPHIRE-II: Treatment-experienced HCV Genotype 1 patients without cirrhosis[3]

- Double-blind, placebo-controlled trial
- Randomization in 3:1 ratio to receive ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 12 weeks or placebo for 12 weeks. Stratified by HCV genotype (1a vs non-1a) and prior response to peginterferon/ribavirin (i.e., relapse, partial response or null response).
- Following 12 weeks of double-blind part of trial, the placebo arm received ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 12 weeks (open-label).
- Demographics of the arm randomized to ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 12 weeks (n=297) included mean age 51.7 years old (range: 19 to 71); 56.2% male; 90.6% white, 7.4% black; 7.4% Hispanic; baseline mean HCV RNA 6.55 $\log_{10}$IU/mL; 58.2% Genotype 1a; 11.4% *IL28B* CC genotype; and 32.0% with Fibrosis score 2 or 3; type of prior response (29.0% relapser, 21.9% partial response and 49.2% null response).

PEARL-II: Treatment-experienced HCV Genotype 1b patients without cirrhosis[4]

- Open-label
- Randomization in 1:1 ratio to receive ombitasvir, paritaprevir/ritonavir plus dasabuvir *with* ribavirin for 12 weeks or ombitasvir, paritaprevir/ritonavir plus dasabuvir *without* ribavirin for 12 weeks. Stratified by prior response to peginterferon/ribavirin (i.e., relapse, partial response or null response).
- Demographics of the arm randomized to ombitasvir, paritaprevir/ritonavir plus dasabuvir *with* ribavirin for 12 weeks (n=91) included mean age 54.2 years old (SD: ±10.9); 49.5.% male; 92.3% white, 3.3% black; 4.4% Hispanic; baseline mean HCV RNA 6.56 ±0.56 $\log_{10}$IU/mL; 11.0% *IL28B* CC genotype; and Fibrosis score (70.3% with F0 or F1; 14.3% with F2; 15.4% with F3); type of prior response to peginterferon/ribavirin (36.3% relapser, 28.6% partial response and 35.2% null response).
- Demographics of the arm randomized to ombitasvir, paritaprevir/ritonavir plus dasabuvir *without* ribavirin for 12 weeks (n=95) included mean age 54.2 years old (SD: ±10.5); 60.0% male; 90.5% white, 6.3% black; 2.1% Hispanic; baseline mean HCV RNA 6.48 ±0.53 $\log_{10}$IU/mL; 7.4% *IL28B* CC genotype; and Fibrosis score (64.2% with F0 or F1; 22.1% with F2; 13.7% with F3); type of prior response to peginterferon/ribavirin (36.8% relapser, 28.4% partial response and 34.7% null response).

PEARL-III and IV: Treatment-naïve HCV Genotype 1b patients without cirrhosis (PEARL-III) and Treatment-naïve HCV Genotype 1a patients without cirrhosis (PEARL IV)[5]

- Double-blind
- Randomization in 1:1 ratio for Genotype 1b and 1:2 for Genotype 1a to receive ombitasvir, paritaprevir/ritonavir plus dasabuvir *with* ribavirin for 12 weeks or ombitasvir, paritaprevir/ritonavir plus dasabuvir *without* ribavirin (i.e., placebo) for 12 weeks. Stratified by and *IL28B* genotype (CC vs non-CC).
- Demographic: Refer to published article.

TURQUOISE-II: Treatment-naïve and -experienced HCV Genotype 1 patients with cirrhosis[6]

- Open-label

- Randomization in 1:1 ratio to receive ombitasvir, paritaprevir/ritonavir plus dasabuvir *with* ribavirin for 12 weeks or ombitasvir, paritaprevir/ritonavir plus dasabuvir *with* ribavirin for 24 weeks. Stratification for treatment-naïve patients was by HCV genotype (1a vs 1b) and *IL28B* genotype (CC vs non-CC). Stratification for treatment-experienced patients was by HCV genotype (1a vs 1b) and prior response to peginterferon/ribavirin (i.e., relapse, partial response or null response).
- Demographics: Refer to published article.
- SVR based upon HCV Genotype subtype 1a vs 1b with further stratification of treatment-naïve and –experienced are shown in Table 3. The FDA approved indication for patients with HCV Genotype 1a with cirrhosis is ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 24 weeks and patients with HCV Genotype 1b with cirrhosis is ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 12 weeks. However, based on these data (Table 3), 12 weeks of treatment with ombitasvir, paritaprevir/ritonavir plus dasabuvir may be considered in Genotype 1a cirrhotic patients who are naïve or in whom prior relapse or partial response to previous peginterferon/ribavirin treatment has been documented and confirmed.

Table 3. SVR at 12 weeks in patients with cirrhosis, by HCV Genotype subtype (1a vs 1b) and treatment experience.

	SVR at 12 weeks	
Subgroups	**Ombitasvir, paritaprevir/ritonavir plus dasabuvir *with* ribavirin 12 week regimen (n=208)**	**Ombitasvir, paritaprevir/ritonavir plus dasabuvir *with* ribavirin 24 week regimen (n=172)**
HCV Genotype 1a		
Treatment-naïve	92.2% (59/64)	92.9 (52/56)
Treatment-experienced with peginterferon/ribavirin		
Relapse	93.3% (14/15)	100% (13/13)
Partial response	100% (11/11)	100% (10/10)
Null response[a]	80.0% (40/50) (95% CI 68.9 to 91.1)	92.9% (39/42) (95% CI 85.1 to 100)
HCV Genotype 1b		
Treatment-naïve	100% (22/22)	100% (18/18)
Treatment-experienced with peginterferon/ribavirin		
Relapse	100% (14/14)	100% (10/10)
Partial response	85.7% (6/7)	100% (3/3)
Null response	100% (25/25)	100% (20/20)

Liver Transplant Recipients (CORAL-I)[1,7]

In an open-label, phase 2 trial, the use of ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 24 weeks was evaluated in 34 liver transplant recipients infected with HCV Genotype 1. Ribavirin dose was determined by the investigator; the most common dosage regimen at initiation and end of therapy was 600 to 800mg. Inclusion included 12 months post-transplant, normal hepatic function and Fibrosis Score ≤2. Demographics included mean age of 59.6 ±6.6 years old, 29/34 (85%) with GT1a; immunosuppressants (85% on tacrolimus; 15 on cyclosporine); and median time since transplant 39.5 months. SVR12 was achieved in 33 of the 34 patients (97%). Please refer to drug-interaction section for significant interactions with immunosuppressants (i.e. requires dosage adjustment and close monitoring for subsequent dosage modifications) and other medications.

HCV/HIV co-infected (TURQUOISE-I)[1]

In an open-label trial, the use of ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin for 12 or 24 weeks was evaluated in 63 patients co-infected with HCV Genotype 1 and HIV. Inclusion included stabilized on certain antiretroviral regimens including ritonanvir-boosted atazanavir or raltegravir with tenofovir plus emtricitabine or lamivudine. Note that patients receiving ritonanvir-boosted atazanavir stopped the ritonavir as part of HIV regimen when therapy with ombitasvir, paritaprevir/ritonavir plus dasabuvir was initiated; ritonavir was re-initiated following completion of ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen. Demographics included median age of 51 years old (31 to 69); 24% black; 19% with compensated cirrhosis; 67% HCV treatment-naïve; 89% with HCV G1a infection. SVR12 was achieved in 51 of the 56 (91%) patients with HCV GT1a infection and 7 of the 7 patients with HCV GT1b infection.

Summary of efficacy

- The FDA approved regimens for ombitasvir, paritaprevir/ritonavir plus dasabuvir with or without ribavirin with or without ribavirin achieved SVR rates in the range of 95-100% (Table 1).

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, 5 or 6

Safety (for more detailed information refer to the product package insert)[1,5]

	Comments
Boxed Warning	• None
Contraindications	• If co-administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. • Patients with severe hepatic impairment. • Co-administration with drugs that are1) highly dependent on CYP3A for clearance; 2) strong inducers of CYP3A and CYP2C8; OR 3) and strong inhibitors of CYP2C8. • Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome).
Warnings/Precautions	• ALT Elevations: discontinue ethinyl estradiol-containing medications prior to starting ombitasvir, paritaprevir/ritonavir plus dasabuvir (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. • If co-administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen. • Co-administration of certain other drugs may result in known or potentially significant drug interactions.

Safety Considerations

The safety assessment was based on pooled data in more than 2,000 HCV infected genotype 1 patients with compensated liver disease from six Phase 3 clinical trials.

Adverse Reactions

Common adverse reactions	• In patients without co-administration of ribavirin, the most common adverse reactions (≥5%) were nausea, pruritus and insomnia. • In patients co-administered ribavirin, the most common adverse reactions (≥10%) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia.
Death/Serious adverse reactions	Deaths were not discussed in the prescribing information. SAPPHIRE I & II: 2% experienced SAEs. PEARL II, III, & IV: SAEs were not discussed in PI TURQUOISE II: 6% for 12 week regimen and 5% for 24 week regimen
Discontinuations due to adverse reactions	SAPPHIRE I & II: <1% PEARL II, III, & IV: <1% for Viekira with ribavirin and <1% for Viekira without ribavirin TURQUOISE II: 2% for 12 week arm and 5% for 24 week arm
Laboratory Abnormalities	**Serum ALT elevations:** 1% of patients treated with Viekira Pak experienced ALT levels >5X ULN after starting treatment. In patients receiving concomitant ethinyl estradiol containing medications, the incidence was 25% (4/16). In patients receiving estradiol and conjugated estrogens (i.e. not ethinyl estradiol), the incidence of clinically relevant ALT elevations was 3% (2/59). The majority of ALT elevations were considered drug-related liver injury. Cirrhosis was not a risk factor.

Bilirubin elevations: 15% of patients treated with Viekira Pak *with* ribavirin and 2% treated with Viekira *without* ribavirin experienced bilirubin levels at least 2X ULN after starting treatment. 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.

Anemia/Decreased Hemoglobin: Hemoglobin levels in patients treated with Viekira Pak *with and without* ribavirin were -2.4 g/dL and -0.5 g/dL, respectively. Less than 1% of patients treated with Viekira Pak with ribavirin had hemoglobin levels decrease to <8.0 g/dL during treatment; one patient discontinued therapy due to anemia. No patients treated with Viekira Pak alone had a hemoglobin level less than 10 g/dL.

Liver Transplant patients receiving Viekira Pak with ribavirin (n=34): Adverse events (>20%) included fatigue 50%, headache 44%, cough 32%, diarrhea 26%, insomnia 26%, asthenia 24%, nausea 24%, muscle spasms 21% and rash 21%. Ten subjects (29%) had at least one post-baseline hemoglobin value of less than 10 g/dL. Ten subjects underwent a ribavirin dose modification due to decrease in hemoglobin and 3% (1/34) had an interruption of ribavirin. Five subjects received erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No subject received a blood transfusion.

HIV patients receiving Viekira Pak with ribavirin, stabilized on certain antiretrovirals (n=69):

- Most common adverse events (>10%) included fatigue (48%), insomnia (19%), nausea (17%), headache (16%), pruritus (13%), cough (11%), irritability (10%), and ocular icterus (10%).
- Elevations in total bilirubin greater than 2 x ULN (mostly indirect) occurred in 34 (54%) patients; 15 of the 34 were also receiving atazanavir at the time of bilirubin elevation and 9 of these patients also had adverse events of ocular icterus, jaundice or hyperbilirubinemia. None of the subjects with hyperbilirubinemia had concomitant elevations of aminotransferases.
- No co-infected patient experienced a grade 3 ALT elevation.
- 7 patients (11%) had at least one post-baseline hemoglobin value <10 g/dL, and 6 of these patients had a ribavirin dose modification (and none required a blood transfusion or erythropoietin).
- Median CD4 counts decline of 47 cells/mm^3 and 62 cells/mm^3 were observed at the end of 12 and 24 weeks of treatment, respectively, and most returned to baseline levels post-treatment. Two subjects had CD4 counts decrease to <200 cells/mm^3 during treatment without a decrease in CD4%.

Drug-Drug Interactions[1]

- Consult the prescribing information prior to use for potential drug interactions and on-going evaluation.
- Ombitasvir, paritaprevir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Co-administration with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.
- Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes and co-administration with strong CYP3A inhibitors may increase concentrations of paritaprevir and ritonavir. Dasabuvir is primarily metabolized by CYP2C8 enzymes and co-administration with CYP2C8 inhibitors may increase concentrations of dasabuvir. Ombitasvir is primarily metabolized via amide hydrolysis while CYP enzymes play a minor role in its metabolism. Ombitasvir, paritaprevir, dasabuvir and ritonavir are substrates of P-gp. Ombitasvir, paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may increase the plasma concentrations of the various components of HCV regimen.

- Co-administration of the following drugs is contraindicated: alfuzosin, carbamazepine, phenytoin, phenobarbital**,** gemfibrozil, rifampin, ergotamine dihydroergotamine, ergonovine, methylergonovine, ethinyl estradiol-containing medications, St. John's wort, lovastatin, simvastatin, pimozide, efavirenz, sildenafil when dosed for the treatment of pulmonary arterial hypertension, triazolam, and midazolam (i.e., orally administered).
- Co-administration of the following drugs is not recommended voriconazole (unless benefit outweighs risk), darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, salmeterol,
- For immunosuppressants,
    - Cyclosporine: the prescribing information recommends when initiating therapy with Viekira Pak to 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 Viekira Pak therapy, the appropriate time to resume pre-Viekira Pak 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: the prescribing information recommends when initiating therapy with Viekira Pak, the dose of tacrolimus needs to be reduced. Do not administer tacrolimus on the day Viekira Pak is initiated. Beginning the day after Viekira Pak 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 Viekira Pak therapy, the appropriate time to resume pre-Viekira Pak dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus related side effects is recommended.
- Other potentially significant drug interactions may include antiarrhythmics (e.g., amiodarone, bepridil, disopyramide, flecainide, etc), ketoconazole, amlodipine, fluticasone, furosemide, atazanavir/ritonavir, rosuvastatin, pravastatin, buprenorphine, norbuprenorphine, omeprazole, alprazolam. Please refer to prescribing information for additional detail to manage these drug interactions.

Risk Evaluation

As of December 2014	Comments
Sentinel event advisories	• None for combination product
Look-alike/sound-alike error potentials	• Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List):

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Ombitasvir, paritaprevir, and ritonavir 12.5/75/50-mg fixed-combination tab + dasabuvir 250mg tab	None	None	None	None for fixed-dose combination. If listed alphabetically, dasabuvir as single agent has LASA potential with **denavir**. If fixed dose combination ingredients are listed first alphabetically, ombitasvir has LASA potential with **oseltamivir**
Viekira Pak	None	none	None	Viagra Viokace

Other Considerations

- None

Dosing and Administration[1]

Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg co-formulated tablets once daily (in the morning) **and** one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content. For certain patient populations, co-administration with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day) is recommended. **Treatment regimen and duration based upon patient characteristics as described in the Table below.**

NOTE: Viekira Pak consists of ombitasvir, paritaprevir, ritonavir fixed dose combination tablets co-packaged with dasabuvir tablets. Each weekly carton contains seven daily dose packs. Each daily dose pack contains four tablets: two 12.5/75/50 mg ombitasvir, paritaprevir, ritonavir tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening.

Population includes HCV monoinfected or HCV/HIV-1 co-infected stabilized on certain antiretroviral regimens[a,b,]	Dosage Regimens	Total treatment duration
Genotype 1a without cirrhosis	Viekira Pak plus ribavirin	12 weeks
Genotype 1a with cirrhosis	Viekira Pak plus ribavirin	24 weeks[c]
Genotype 1b without cirrhosis	Viekira Pak	12 weeks
Genotype 1b with cirrhosis	Viekira Pak plus ribavirin	12 weeks
Liver Transplant receipts with normal hepatic function and mild fibrosis (Metavir fibrosis ≤2)[d]	Viekira Pak plus ribavirin	24 weeks

[a]Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
[b]Population includes treatment-naïve and treatment-experienced patients with peg/ribavirin.
[c]Viekira Pak plus ribavirin for 12 weeks may be considered for patients who are treatment naïve OR in patients with prior relapse or partial response to previous peginterferon/ribavirin treatment; Refer to Efficacy Section for more detail.
[d]Dosage adjustments are necessary with cyclosporine or tacrolimus; Refer to drug interactions.

Special Populations (Adults)[1]

	Comments
Elderly	• Clinical trials included 174 subjects aged 65 and over. No overall differences in safety or effectiveness were observed.
Pregnancy	• Pregnancy Category B: Adequate and well controlled studies 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, ritonavir (mice and rats), or dasabuvir (rats and rabbits) at exposures higher than the recommended clinical dose. Because animal reproduction studies are not always predictive of human response, this regimen should be used during pregnancy only if clearly needed. • If ombitasvir, paritaprevir/ritonavir plus dasabuvir 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 in pregnancy.
Lactation	• It is not known whether any of the components or their metabolites are present in human milk. Unchanged ombitasvir, paritaprevir and its hydrolysis product M13, and dasabuvir 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 ombitasvir, paritaprevir/ritonavir plus dasabuvir and any potential adverse effects on the breastfed child from ombitasvir, paritaprevir/ritonavir plus dasabuvir or from the underlying maternal condition. • If ombitasvir, paritaprevir/ritonavir plus dasabuvir is administered with ribavirin, the nursing mothers information for ribavirin applies to this combination regimen (see prescribing information for ribavirin).
Renal Impairment	• No dosage adjustment of ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen 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 <30ml/min or for hemodialysis use 200mg daily.
Hepatic Impairment	• No dosage adjustment in patients with mild hepatic impairment (Child-Pugh A). It is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and contraindicated in patients with severe hepatic impairment (Child-Pugh C).
Pharmacogenetics/genomics	• No data identified in prescribing information.
HIV co-infected patients	• Ritonavir is also an HIV-1 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/ritonavir plus dasabuvir regimen should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance. However, potential antiretroviral regimens that can be co-administered with the ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen need to be carefully evaluated prior to initiation of the HCV regimen. Antiretroviral regimens evaluated in clinical studies which may be acceptable include tenofovir/emtricitabine in combination with either atazanavir 300mg (without ritonavir) once daily or raltegravir 400mg twice daily. Antiretroviral regimens containing efavirenz, darunavir/ritonavir, lopinavir/ritonavir or rilpivirine are <u>not</u> recommended.

Projected Place in Therapy

- The VHA Office of Public Health HCV Registry Reports indicates that there were 174,302 Veterans with HCV viremia in VHA care in 2013. More specifically, there were 89,703 HCV Genotype 1 monoinfected viremic Veterans and 3,465 HCV Genotype 1-HIV co-infected Veterans in VHA care in 2013.[8-10]
- Ombitasvir, paritaprevir/ritonavir plus dasabuvir with or without ribavirin is an interferon-free regimen for the treatment of HCV Genotype 1 patients. It is available as a fixed-dosed combination of ombitasvir, paritaprevir, and ritonavir co-packaged with dasabuvir. Ritonavir is included in the fixed-dose combination as a pharmacokinetic enhancer (i.e., increases drug concentration of paritaprevir due to ritonavir's ability to potently inhibit CYP3A). The dosage regimen is two tablets of the fixed-dosed combination of ombitasvir, paritaprevir, ritonavir once daily and one dasabuvir tablet twice daily with food. Co-administration of ribavirin is recommended in patients infected with HCV Genotype 1a with or without cirrhosis as well as HCV Genotype 1b with cirrhosis. Duration of therapy ranges 12 to 24 weeks depending on patient characteristics.
- The FDA approved regimens for ombitasvir, paritaprevir/ritonavir plus dasabuvir with or without ribavirin with or without ribavirin achieved SVRs in the range of 95-100% . [Overall Quality of Evidence: High (Refer to Appendix A; note all pivotal clinical trials sponsored by Abbvie].
- Pooled safety data are available from six Phase 3 clinical trials. In patients without co-administration of ribavirin, the most common adverse reactions (≥5%) were nausea, pruritus and insomnia. In patients with co-administered ribavirin, most common adverse reactions (≥10%) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. Laboratory abnormalities included ALT and bilirubin elevations.
- Ombitasvir, paritaprevir/ritonavir plus dasabuvir have significant drug-interactions; therefore, patient should be assessed for potential drug-interactions at baseline and throughout therapy. Notably, the co-administration of certain antiretrovirals including efavirenz, darunavir/ritonavir, lopinavir/ritonavir or rilpivirine are <u>not</u> recommended with ombitasvir, paritaprevir/ritonavir plus dasabuvir and immunosuppressants (cyclosporine and tacrolimus) require dosage adjustments and monitoring to determine subsequent dosage regimen.

References

1. Viakera [package insert]. AbbVie, Inc., North Chicago, IL; December 2014.
2. Feld JJ, Kowdley KV, Coakley E et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1594-603.
3. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1604-14.
4. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology. 2014;147:359-365.
5. Ferenci P[1], Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370:1983-92.
6. Poordad F[1], Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014;370:1973-82.
7. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014:371:2375-82.
8. Office of Public Health Hepatitis C Infection Status of Hepatitis C Registry Patients 2013 http://vaww.hepatitis.va.gov/data-reports/ccr2013/Demo-HCV3PopInCare-Jan14-HCV-2013-All.asp
9. Office of Public Health Prior Treatment Status and Cirrhosis/ALD (FIB-4) Status of HCV Monoinfected Genotype 1 Veterans in VHA Care: 2013 http://vaww.hepatitis.va.gov/data-reports/ccr2013/DAA-EligibleFIB4CurInCare-Jan14-HCVVirMonoGT1-2013-All.asp
10. Office of Public Health Prior Treatment Status and Cirrhosis/ALD (FIB-4) Status of HCV/HIV Coinfected Genotype 1 Veterans in VHA Care: 2013 http://vaww.hepatitis.va.gov/data-reports/ccr2013/DAA-EligibleFIB4CurInCare-Jan14-CI-HIVPARV-HCVVirGT1-2013-All.asp

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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