

Ombitasvir, Paritaprevir/Ritonavir and Dasabuvir (Viekira Pak™)

Criteria for Use

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

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES. The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive this regimen without local adjudication.*

- Limited Life Expectancy (refer to issues for consideration)
- Documented ongoing nonadherence to prescribed medications or medical treatment, failure to complete hepatitis C virus (HCV) disease evaluation appointments and procedures or unable to commit to scheduled follow-up/monitoring for the duration of treatment
- Known hypersensitivity to ombitasvir, paritaprevir, ritonavir, or dasabuvir or any other component of this direct acting antiviral based-regimen
- Co-administration of drugs 1) highly dependent on CYP3A for clearance such as lovastatin and simvastatin and for which elevated plasma concentrations are associated with serious and/or life-threatening events; 2) drugs that are strong inducers of CYP3A and CYP2C8 such as rifampin or St. John's wort and may lead to reduced efficacy of ombitasvir, paritaprevir/ritonavir and dasabuvir; OR 3) drugs such as gemfibrozil that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation
- Patient receiving ethinyl estradiol containing product(s)
- HIV/HCV co-infection in patients not receiving antiretroviral therapy OR where antiretroviral drug-interactions preclude the use of ombitasvir, paritaprevir/ritonavir plus dasabuvir such as efavirenz, darunavir/ritonavir, lopinavir/ritonavir or rilpivirine (Refer to Issues for Consideration)
- Decompensated liver disease (i.e., Child-Pugh score ≥ 7 (i.e. Class B or C), MELD score ≥ 15 , and/or clinical manifestations)
- Previous virologic failure to NS3-4A protease-inhibitor, sofosbuvir-containing regimen or NS5a inhibitors (i.e. ledipasvir, ombitasvir, daclatasvir)
- HCV **genotype 2, 3, 4, 5 or 6** infection (For Genotype 4, refer to Issues for Consideration)

When ombitasvir, paritaprevir/ritonavir and dasabuvir is used in combination with ribavirin:

- Contraindication and/or intolerance to ribavirin
 - Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, autoimmune hepatitis, hemoglobinopathies) and/or intolerance (i.e. baseline hemoglobin $< 12\text{g/dL}$) and/or history of *significant* adverse events with previous ribavirin-containing regimen. **Please note that history of anemia related to ribavirin-containing regimen should be evaluated in context of PBM CFU for ESA (i.e., ribavirin dose reduction to 600mg must have been instituted prior to consideration of ESA use) and does not necessarily constitute intolerance.

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

- Treatment regimen and duration according to the dosage and administration section below
- Under care of and/or in collaboration with an experienced VA HCV practitioner
- Adherence counseling performed including laboratory follow-up and documented understanding by patient
- Hepatitis C Virus Genotype 1 infection**

For women of childbearing potential receiving ribavirin or who have a male partner receiving ribavirin

- When the ombitasvir, paritaprevir/ritonavir and dasabuvir regimen is used in combination with ribavirin therapy (which is pregnancy category X), it should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Two effective methods of contraception should be used during treatment with ombitasvir, paritaprevir/ritonavir and dasabuvir and concomitant ribavirin, and for 6 months after treatment has concluded. Note: the co-administration of ethinyl estradiol-containing medications are contraindicated due to potential increase in liver function tests and must be discontinued prior to starting of ombitasvir, paritaprevir/ritonavir plus dasabuvir therapy. Alternative methods of contraception (e.g., progestin-only contraception or non-hormonal methods) are recommended. Routine monthly pregnancy tests must be performed during HCV therapy.

Dosage, 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 without regard to fat or calorie content. For certain patient populations, co-administration with ribavirin (in 2 divided doses) with food ($< 75\text{ kg}$: 1000 mg/day or $\geq 75\text{ kg}$: 1200 mg/day) is recommended. **Treatment regimen and duration are based upon patient characteristics as described in the Table below.**

NOTE: Viekira Pak consists of ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged 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 patients with HCV monoinfected, HCV/HIV-1 co-infected stabilized on certain antiretroviral regimens or hepatocellular carcinoma (HCC) ^{a,b,c}	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 ^d
Genotype 1b without cirrhosis	Viekira Pak	12 weeks
Genotype 1b with cirrhosis	Viekira Pak plus ribavirin	12 weeks

^aRefer to Issues for consideration for alternative treatment options including pre- and post-transplant patients

^bFollow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

^cPopulation includes treatment-naïve and treatment-experienced patients with peginterferon/ribavirin.

^dViekira 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 Issues for Consideration for more detail.

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving HCV therapy, the following monitoring is recommended for ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen:

- **Baseline and on-going evaluation for potential drug-drug interactions:** Patient should be assessed for potential drug-interactions including over the counter products.
- **Hematologic adverse events (anemia) if co-administered with ribavirin:** Complete blood count with white blood cell differential counts should be obtained at baseline and at treatment weeks 2, 4, 8, and 12, and at other time points, as clinically appropriate. Initial management of anemia should consist of ribavirin dose reduction to 600mg for hemoglobin <10g/dL or sooner if clinically indicated; for additional monitoring and management of Hepatitis C treatment-related anemia refer to the PBM CFU for Recombinant Erythropoietin.
- **ALT Elevations:** Monitor liver chemistry tests before initiating and during therapy.
- **Careful virologic monitoring** should be assessed to avoid the emergence of resistance. Patients should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 log₁₀ IU/mL from nadir), discontinuation of all therapy should be strongly considered.
- **Sustained Viral Response (SVR) or relapse** should be determined by measurement of HCV RNA at the end of therapy and 12 weeks thereafter.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.
- **Monthly pregnancy tests** for women of childbearing potential receiving ribavirin

Issues for Consideration

Treatment Considerations:

- **In genotype 1a patients with cirrhosis, SVR rates varied by prior treatment history.** In genotype 1a naïve patients with cirrhosis, SVR rates were 92% (59/64) with 12 weeks and 95% (53/56) with 24 weeks of therapy. In prior relapsers treated with ombitasvir, paritaprevir/ritonavir plus dasabuvir, SVR rates were 93% (14/15) in those treated for 12 weeks and 100% (13/13) in those treated for 24 weeks. In prior partial responders, SVR rates were 100% in patients treated for either 12 weeks (11/11) or 24 weeks (10/10). In prior null responders, SVR rates were 80% (40/50) for those treated for 12 weeks and 93% (39/42) for those treated for 24 weeks. **Based on these data, 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. Consider extending to 24 weeks for slow on-treatment virologic response on a case-by-case basis.**
- **In genotype 4 patients,** an open-label phase IIb study of 86 treatment-naïve and -experienced patients who received ombitasvir, paritaprevir/ritonavir ± RBV for 12 weeks, SVR was achieved in 100% (42/42) and 91% (40/44) in naïve patients who received treatment with and without RBV and in 100% (49/49) of experienced patients who received ombitasvir, paritaprevir/ritonavir plus RBV for 12 weeks. This regimen is not FDA approved for the treatment of GT4 infection.
- **Populations unlikely to benefit from HCV treatment:** According to AASLD/IDSA HCV Guidelines, “patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment. Chronic hepatitis C is associated with a wide range of comorbid conditions. Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.”
- **Chronic HCV-infected patients with minimal fibrosis** (METAVIR stage 0 or 1 based on an adequate liver biopsy specimen) and no other risk factors for liver disease are at lower risk for developing advanced liver disease in the short-term. After a thorough discussion of prognosis and treatment options, the provider and patient may agree to observation and defer treatment. Treatment should be reconsidered if liver disease progresses. Modifiable risk factors for progression of liver disease, such as alcohol use, should be addressed.
- **In genotype 1 patients who had previous virological failure with a NS3-4A protease inhibitor or sofosbuvir-based regimen,** ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen has not been studied and therefore, cannot be recommended.

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- **HIV: Co-infected patients should be managed in consultation with an experienced HIV treatment provider. Due to potential drug interactions with antiretrovirals and co-formulation with ritonavir, alternative treatment with ledipasvir/sofosbuvir is recommended in patients not receiving antiretroviral therapy OR where antiretroviral drug-interactions preclude the use of ombitasvir, paritaprevir/ritonavir plus dasabuvir (refer to ledipasvir/sofosbuvir CFU).** Ritonavir is also an HIV-1 protease inhibitor and can select for HIV protease inhibitor resistance-associated substitutions; the HIV status of all patients receiving this regimen should be known prior to the initiation of therapy to avoid inadvertently giving ritonavir-monotherapy to an unrecognized HIV infected patient. 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 not recommended.
 - **Decompensated cirrhosis:** No efficacy and safety data are available; **alternative treatment with ledipasvir/sofosbuvir plus ribavirin in patients with Genotype 1 is recommended (refer to ledipasvir/sofosbuvir CFU).**
 - **Hepatocellular carcinoma (HCC) or other cancer:** It is reasonable to treat HCV in any patient with HCC or other malignancy *if there is a high likelihood that the cancer has been cured*. Curative treatments for solitary or early stage HCCs within Milan criteria include resection and thermal ablation as well as liver transplantation (TACE, radioembolization, radiation therapy and targeted/chemotherapy are NOT considered curative). For those receiving resection or thermal ablation, if staging studies indicate good likelihood of success (absence of macrovascular invasion, clear margins, etc.) and if follow-up restaging studies show no evidence of cancer recurrence, then treatment of HCV should be offered.
 - **Hepatic Impairment:** No dosage adjustment in patients with mild hepatic impairment (Child-Pugh A). The ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C).
 - **Pre-Liver transplant (also see decompensated cirrhosis and HCC bullet above): The decision to treat any patient awaiting transplantation should be made in consultation with the transplant center where the patient is listed and determined on a case by case basis.** Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (pre- or post-) or whether treatment is appropriate given patient's prognosis.
 - **Post-Liver Transplant:** Although Viekira Pak is approved by the FDA for use in patients who have received a liver transplant, limited efficacy and safety data are available in this population. The ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen + ribavirin for 24 weeks was evaluated in 34 post-liver transplant patients with HCV genotype 1 infection and fibrosis stages F0 through F2. SVR was achieved in 97.1% (33/34) with 1 patient relapse. Most patients received ribavirin doses of 600mg or 800mg/day; all patients with ribavirin dose reductions achieved SVR. In this study, tacrolimus was administered at a dose of 0.5mg every week or 0.2mg every three days; cyclosporine was administered as one-fifth of the daily pre-treatment dose; prednisone was dosed at <5mg/day. Based upon these data, the prescribing information states the recommended duration of ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin is 24 weeks for liver transplant recipients infected with HCV genotype 1 with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower). Dosage adjustment of calcineurin inhibitors is needed. **Due to significant interactions with ritonavir, alternative treatment with ledipasvir/sofosbuvir plus ribavirin in patients with Genotype 1 is recommended to minimize potential for interactions (refer to ledipasvir/sofosbuvir CFU).**
 - **Renal Impairment:** No dosage adjustment of the 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.
 - **Substance or Alcohol Use:** All patients should be evaluated for current alcohol and other substance use, with validated screening instruments. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists as needed. **Thus, automatic disqualification of patients as treatment candidates based on a specific length of abstinence is unwarranted and is strongly discouraged.**
 - **Mental Health Conditions:** HCV-infected patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. The use of interferon-containing regimens is associated with worsening of these conditions. Patients should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.
 - **Hepatitis B:** No safety and efficacy data are available in this population; prescribing information states that no dosage adjustments are needed in patients receiving tenofovir. No pharmacokinetic data are available for entecavir or lamivudine when co-administered with the ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen.
- Drug-interactions (Refer to full prescribing information for details):**
- 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.

Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use and limiting acetaminophen use to no more than 2g/day.
- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if appropriate.
- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site <http://vaww.hepatitis.va.gov>

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