OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR

<table>
<thead>
<tr>
<th>Generic Structure</th>
<th>Brand Name</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
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<tr>
<td>OMBITASVIR/PARITAPREVIR/RITONAVIR/...</td>
<td>VIEKIRA PAK</td>
<td>41644</td>
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</table>

This drug requires a written request for prior authorization. All requests for hepatitis C medications require review by a pharmacist prior to final approval.

GUIDELINES FOR USE

1. Has the patient previously failed a short trial with Harvoni (e.g. adverse effect early in therapy)? **[Note: An individual who has completed a full course of therapy with Harvoni that did not achieve SVR will not be approved.]**
   - If yes, continue to #2.
   - If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

2. Does the patient have one or more of the following conditions?
   - Decompensated liver disease
   - Severe liver impairment (Child-Pugh C)
   - A limited life expectancy (less than 12 months) due to non-liver related comorbid conditions (e.g. physician attestation)
   - Patient is on hemodialysis
   - Concurrent use with any of these (contraindicated or not recommended by the manufacturer) medications: alfuzosin, carbamazepine, phenytoin, phenobarbital, gemfibrozil, rifampin, ergotamine dihydroergotamine, ergonovine, methylergonovine, ethinyl estradiol containing medications (such as combined oral contraceptives, Nuvaring, Ortho Evra or Xulane transdermal patch system), St. John’s Wort, lovastatin, simvastatin, pimozide, efavirenz, Revatio (sildenafil dose of 20mg and/or dosed TID for PAH), triazolam, oral midazolam, darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, salmeterol
   - Prior use (failure of a full course of therapy) or concurrent use of any HCV protease inhibitors including Olysio (simeprevir), Victrelis (boceprevir), or Incivek (telaprevir)
   - Prior use (failure of a full course of therapy) or concurrent use of any NS5B polymerase inhibitor including Sovaldi (sofosbuvir)
   - Prior use (failure of a full course of therapy) of concurrent use of any NS5B polymerase inhibitor/NS5A inhibitor including Harvoni (ledipasvir/sofosbuvir)
   - If yes, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.
   - If no, continue to #3.

CONTINUED ON NEXT PAGE
OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR

GUIDELINES FOR USE (CONTINUED)

3. Does the patient have evidence of hepatitis C infection (e.g. at least two detectable HCV RNA levels separated by 6 months), or if patient has acute infection, has the patient received monitoring of HCV RNA for at least 6 months, with at least two detectable HCV RNA levels over the past 6 months (separated by 6 months)? (Note: If patient has evidence of prescriptions for past treatment for hepatitis C, one detectable HCV RNA level within the last 6 months is acceptable.)

   If yes, continue to #4.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

4. Does the patient meet the following criteria:
   - patient at least 18 years of age
   - hepatitis C, genotype 1
   - patient currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (for example, a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model

   If yes, continue to #5.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

5. Has the patient been evaluated to be absent of current alcohol and other substance abuse, with 1) validated screening instruments (e.g., AUDIT or AUDIT C) or via physician attestation **AND** 2) a urine toxicology screen at baseline?

   If yes, continue to #6.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

**CONTINUED ON NEXT PAGE**
GUIDELINES FOR USE (CONTINUED)

6. Does the patient have evidence of fibrosis stage 3 or 4 as determined by any **ONE** of the following:
   - Metavir score F3 or F4 from liver biopsy
   - APRI score above 1.5
   - Radiological Imaging consistent with cirrhosis
   - Evidence from physical exam and clinical findings consistent with cirrhosis
   - Fibroscan score of 9.5kPa or higher
   - Fibrotest result of 0.58 or higher

   If yes, continue to #8.
   If no, continue to #7.

7. Does the patient have Metavir Stage 2 with another condition listed as “high priority” or “highest priority” for treatment, such as liver transplant recipient, severe extra-hepatic hepatitis C, other co-existing liver disease such as non-alcoholic steatohepatitis, debilitating fatigue, porphyria cutanea tarda, diabetes type 2, hepatitis B, or HIV coinfection?  Note: Metavir Stage 2 can be determined by any one of the following:
   - Metavir score F2 from liver biopsy
   - APRI score above 0.78
   - Fibroscan score of 7.65kPa or higher
   - Fibrotest result of 0.5 or higher

   If yes, continue to #8.
   If no, do not approve.

**DENIAL TEXT:** See the denial text at the end of the guideline.

8. Is the requested medication being used with ribavirin?  [**Note:** Ribavirin combination therapy with Viekira Pak is approved for genotype 1a without cirrhosis, genotype 1a with cirrhosis, and for use in liver transplant patients.]
   
   If yes, continue to #9.
   If no, continue to #15.

9. Is the patient a liver transplant recipient?

   If yes, **approve for 24 weeks by HICL for #112 tablets (1 pack) per 28 days** [**Note:** Approval allows patients with liver transplant recipient to complete a total of 24 weeks of therapy.]
   If no, continue to #10.
10. Does the patient have genotype 1a without cirrhosis?

   If yes, approve for 12 weeks by HICL for #112 tablets (1 pack) per 28 days
   [Note: Approval allows patients with genotype 1a without cirrhosis to complete a total maximum of 12 weeks of therapy.]

   If no, continue to #11.

11. Does the patient have genotype 1a with cirrhosis AND is treatment naïve?

   If yes, approve for 12 weeks by HICL for #112 tablets (1 pack) per 28 days
   [Note: Approval allows treatment naïve patients with genotype 1a with cirrhosis to complete a total maximum of 12 weeks of therapy.]

   If no, continue to #12.

12. Does the patient have genotype 1a with cirrhosis and has received prior treatment (e.g.,
treatment-experienced patient) for hepatitis C with peginterferon and ribavirin? [Note:
Approval not granted for patients with history of prior use of OR concurrent use of HCV protease inhibitors or HCV polymerase inhibitors: Olysio (simeprevir), Victrelis (boceprevir), or Incivek (telaprevir), Sovaldi (sofosbuvir), Harvoni (ledipasvir/sofosbuvir).]

   If yes, continue to #13.

   If no, continue to #15.

13. Is the patient a previous prior relapser or a prior partial responder?

   If yes, approve for a total of 12 weeks by HICL for #112 tablets (1 pack) per 28 days
   [Note: Approval allows patients with genotype 1a that are previous prior relapser or prior partial responders to complete a total of 12 weeks of therapy.]

   If no, continue to #14.

14. Is the patient a treatment-experienced patient and is a previous null responder?

   If yes, approve for 24 weeks by HICL for #112 tablets (1 pack) per 28 days
   [Note: Approval allows patients with genotype 1a that are previous null responders to complete a total of 24 weeks of therapy.]

   If no, do not approve.

   DENIAL TEXT: See the denial text at the end of the guideline.

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OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR

GUIDELINES FOR USE (CONTINUED)

15. Does the patient have genotype 1b?

If yes, approve for 12 weeks by HICL for #112 tablets (1 pack) per 28 days [Note: Approval allows patients with genotype 1b to complete a total of 12 weeks of therapy.]

If no, do not approve.

DENIAL TEXT: See the denial text at the end of the guideline.

DENIAL TEXT: Our guideline for OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR requires that patient meets ALL of the following criteria:

- diagnosis of chronic hepatitis C, genotype 1
- concurrent use with ribavirin unless patient has genotype 1b
- patient is at least 18 years old
- patient is currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (for example, a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model
- inability to tolerate Harvoni
- patient has evidence of fibrosis stage 3 or 4 (Metavir F3 or F4 equivalent) or Metavir F2 with another condition listed as “high priority” or “highest priority” for treatment, such as liver transplant recipient, severe extra-hepatic hepatitis C, other co-existing liver disease such as non-alcoholic steatohepatitis, debilitating fatigue, or porphyria cutanea tarda, diabetes type 2, hepatitis B or HIV coinfection; and
- documentation of HCV infection (e.g., at least two detectable HCV RNA levels) separated by 6 months (or past prescription for treatment of hepatitis C and at least one detectable HCV RNA level).

The medication will NOT be approved for the following patients:

- patient using any of the following medications concurrently while on Viekira Pak: alfuzosin, carbamazepine, phenytoin, phenobarbital, gemfibrozil, rifampin, ergotamine dihydroergotamine, ergonovine, methylergonovine, ethinyl estradiol containing medications (such as combined oral contraceptives, Nuvaring, Ortho Evra or Xulane transdermal patch system), St. John's Wort, lovastatin, simvastatin, pimozide, efavirenz, Revatio, triazolam, oral midazolam, darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, or salmeterol
- patient with decompensated cirrhosis
- patient with severe liver impairment (Child Pugh C) 4
- patient on hemodialysis
- patient must be evaluated for (and absent of) current alcohol and other substance abuse with validated screening instruments (e.g., AUDIT or AUDIT C) or physician attestation AND a urine toxicology screen at baseline

(Denial text continued on next page)
OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR

GUIDELINES FOR USE (CONTINUED)

- patient with limited life expectancy (less than 12 months) due to non-liver related comorbid conditions
- patient with prior use of or concurrent use of a nucleotide NS5B polymerase inhibitor including Sovaldi (sofosbuvir), a combination NS5B polymerase inhibitor/NS5A inhibitor including Harvoni (ledipasvir/sofosbuvir), and a HCV protease inhibitor including Olysio (simeprevir), Victrelis (boceprevir), and Incivek (telaprevir).

A total of 12 weeks of therapy will be approved except 24 weeks of therapy for 1) genotype 1a with cirrhosis if patient a treatment experienced, previous null responder or 2) a liver transplant recipient.

RATIONALE
Ensure appropriate utilization of Viekira Pak (ombitasvir/paritaprevir/ritonavir/dasabuvir).

FDA APPROVED INDICATIONS
For the treatment of chronic hepatitis C genotype 1 infection in adults including those with compensated cirrhosis with or without ribavirin. VIEKIRA PAK includes ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor.

The efficacy of VIEKIRA PAK has not been studied in subjects who have failed prior treatment with another NS5A inhibitor, NS3/4A protease inhibitor, or NS5B inhibitor.

FDA APPROVED DOSAGE
Recommended dosage: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg 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. Ribavirin is also required as part of the regimen, except patients with genotype 1b without cirrhosis.

- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above
- Liver Transplant Recipients: In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2), the recommended duration of VIEKIRA PAK with ribavirin is 24 weeks.

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TREATMENT DURATION & RESPONSE BASED ON TURQUOISE-II:
SVR12 for Chronic HCV Genotype 1-Infected Subjects with Cirrhosis Who Were Treatment-Naïve or Previously Treated with pegIFN/RBV (from Viekira Pak prescribing information)

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Other Information

Genotype 1 is the most common hepatitis C genotype in the U.S. and also the most difficult to treat. Genotype 1 comprises approximately 72% of all hepatitis C cases in the U.S, and is present as genotype subtypes 1a or 1b. Genotype 1a is more common than genotype 1b in the U.S.; genotype 1a accounts for approximately two thirds of all cases of genotype 1 infection and approximately half of all hepatitis C infection in the United States. In Europe, Japan, and China, genotype 1b is more common.

The treatment guidelines recommend that patients with previous failure of any HCV protease inhibitor regimen (triple therapy that included peginterferon/ribavirin or an interferon-free regimen that contained HCV protease inhibitor) should not use regimens containing Olysio (simeprevir) or regimens containing paritaprevir, such as Viekira Pak. Patients with a previous failure of a regimen containing sofosbuvir (Sovaldi or Harvoni) should delay treatment until new therapies are available if possible; for patients with advanced liver fibrosis that cannot delay treatment, the panel recommends a 24-week Harvoni regimen.

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OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR

EFFICACY
Six randomized, multicenter, clinical studies with a total of 2,308 subjects with genotype 1 chronic hepatitis C infection evaluated the efficacy and safety of treatment with Viekira Pak. Patients received a tablet containing ombitasvir, paritaprevir and ritonavir once daily and a dasabuvir tablet twice daily or matching placebo. Treatment experienced patients were defined as prior relapsers, prior partial responders, or prior null responders to peginterferon/ribavirin treatment. For those receiving ribavirin, the dose was 1000mg per day (participants less than 75kg) or 1200mg per day (participants 75kg or greater), divided into twice daily dosing; lower doses of 600mg to 800mg per day were used in the CORAL-1 trial. Ribavirin was dose-adjusted per manufacturer labeling. The primary efficacy endpoint for all studies was SVR, defined as HCV RNA below the lower limit of quantification, at 12 weeks after the end of treatment (SVR12).

Major clinical trials for Viekira Pak (from Viekira Pak prescribing information)

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<thead>
<tr>
<th>Study</th>
<th>Clinical trial design</th>
<th>Patient population</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>SAPPHIRE-I</td>
<td>randomized, multicenter, double-blind</td>
<td>Treatment naïve patients, genotype 1a and 1b, without cirrhosis</td>
<td>1. Viekira Pak + ribavirin OR 2. Placebo</td>
</tr>
<tr>
<td>SAPPHIRE-II</td>
<td>randomized, multicenter, double-blind</td>
<td>Treatment experienced patients, genotype 1a and 1b, without cirrhosis</td>
<td>1. Viekira Pak + ribavirin OR 2. Placebo</td>
</tr>
<tr>
<td>PEARL-II</td>
<td>randomized, multicenter, open-label study</td>
<td>Treatment experienced patients, genotype 1b, without cirrhosis</td>
<td>1. Viekira Pak + ribavirin OR 2. Viekira Pak</td>
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<tr>
<td>PEARL-III</td>
<td>randomized, multicenter, double-blind</td>
<td>Treatment naïve patients, genotype 1b, without cirrhosis</td>
<td>1. Viekira Pak + ribavirin OR 2. Viekira Pak</td>
</tr>
<tr>
<td>PEARL-IV</td>
<td>randomized, multicenter, double-blind</td>
<td>Treatment naïve patients, genotype 1a, without cirrhosis</td>
<td>1. Viekira Pak + ribavirin OR 2. Viekira Pak</td>
</tr>
<tr>
<td>TURQUOISE-II</td>
<td>randomized, multicenter, open-label study</td>
<td>Treatment naïve and treatment experienced patients, genotype 1a and 1b, with cirrhosis</td>
<td>1. Viekira Pak + ribavirin for 12 weeks OR 2. Viekira Pak + ribavirin for 24 weeks</td>
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CORAL-1 | Open-label study | Liver transplant recipients with normal hepatic function and mild fibrosis (Metavir score 2 or below) | 1. All participants received Viekira Pak + ribavirin for 24 weeks

TURQUOISE-I | Randomized, open-label study | Patients with HIV-1 co-infection, 19% had cirrhosis | 1. Viekira Pak for 12 weeks OR 2. Viekira Pak for 24 weeks

- In SAPPHIRE-I and -II, subjects without cirrhosis were randomized to VIEKIRA PAK in combination with ribavirin for 12 weeks or to placebo. Subjects in the placebo arm received placebo for 12 weeks, after which they received open-label VIEKIRA PAK in combination with RBV for 12 weeks.
- In PEARL-II, -III and -IV, subjects without cirrhosis were randomized to receive VIEKIRA PAK with or without RBV for 12 weeks of treatment.
- In the open-label TURQUOISE-II trial, subjects with compensated cirrhosis (Child-Pugh A) who were either treatment-naïve or pegylated interferon/RBV (pegIFN/RBV) treatment experienced were randomized to receive VIEKIRA PAK in combination with RBV for either 12 or 24 weeks of treatment. Subjects who previously failed therapy with a treatment regimen that included VIEKIRA PAK or other direct-acting antiviral agents were excluded.

SAFETY
The most commonly reported adverse reactions (greater than 10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. In subjects receiving VIEKIRA PAK without ribavirin, the most commonly reported adverse reactions (greater than or equal to 5% of subjects) were nausea, pruritus and insomnia.

Viekira Pak is contraindicated in patients with severe hepatic impairment. Other contraindications include hypersensitivity to ritonavir (e.g., toxic epidermal necrolysis, Stevens Johnson syndrome) or for patients concurrently using medications that are strong CYP3A inducers, CYP2C8 inducers or inhibitors, or drugs that are highly dependent on CYP3A4 for clearance. When Viekira Pak is prescribed with ribavirin, prescribers must also consider that contraindications, warnings and precautions for ribavirin will apply.

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SAFETY (CONTINUED)

Drug interactions for Viekira Pak include agents that are strong CYP3A inducers, CYP2C8 inducers or inhibitors, or drugs that are highly dependent on CYP3A4 for clearance. The following medications may decrease serum concentrations of components of Viekira Pak: anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital), rifampin, and St. John’s Wort; concurrent administration of these agents with Viekira Pak is contraindicated. The following medications interact with components of Viekira Pak, and an increase in their concentration may occur with coadministration with Viekira Pak that may lead to toxicity: alfuzosin, gemfibrozil, ergot derivatives, ethinyl estradiol-containing agents, lovastatin, simvastatin, pimozide, efavirenz, sildenafil (when used at doses to treat PAH), triazolam and orally administered midazolam; concurrent administration of these agents with Viekira Pak is contraindicated. The manufacturer also does not recommend concurrent administration of any of the following with Viekira Pak due to significant interactions and potential for toxicity: darunavir/ritonavir, lopinavir/ritonavir, rilvira, and salmeterol. The components of Viekira Pak also have significant drug interactions with cyclosporine and tacrolimus; these immunosuppressants require a dose decrease when starting Viekira Pak, and patients will require serum level monitoring and dose modifications (see Viekira Pak prescribing information for details).

Approximately 1% of patients in clinical trials experienced ALT elevations above five times the upper limit of normal; ALT elevations were typically asymptomatic and occurred during the first four weeks of treatment. Patients using Viekira Pak should receive hepatic laboratory monitoring during the first 4 weeks of therapy and as required after the first 4 weeks. In clinical trials patients using ethinyl estradiol with Viekira Pak had increased incidence of ALT elevations while on therapy. Patients should discontinue any medication containing ethinyl estradiol (e.g., combined oral contraceptives, contraceptive patches, contraceptive transdermal patches, and certain medications used to treat menopause symptoms) prior to beginning therapy with Viekira Pak. Patients should consider discontinuation of Viekira Pak if ALT levels remain above ten times the upper limit of normal. Patients should discontinue treatment with Viekira Pak if ALT elevations occur with signs or symptoms of liver inflammation, or an increase in conjugated bilirubin, alkaline phosphatase, or INR.

In clinical trials the average change in hemoglobin from baseline was -2.4g/dL for patients on Viekira Pak and ribavirin regimen and -0.5g/dL for those on Viekira Pak alone. Hemoglobin decreased during weeks 1-2 of treatment and returned to baseline levels by post-treatment week 4. Overall incidence of anemia in the clinical trials was low; patients using Viekira Pak alone had no incidence of hemoglobin falling to less than 10g/dL, and those using Viekira Pak plus ribavirin had less than 1% with hemoglobin less than 8g/dL. Seven percent of patients using Viekira Pak plus ribavirin required ribavirin dose reduction due to anemia. Three patients required transfusions due to anemia and 5 patients required erythropoietin. One patient discontinued therapy due to severe anemia.

CONTINUED ON NEXT PAGE
OMBITASVIR/PARITAPREVIR/rimonavir/dasabuvir

SAFETY (CONTINUED)
Patients with mild hepatic impairment (Child-Pugh class A) require no dosage adjustment of Viekira Pak. Viekira Pak should not be used for patients with moderate to severe hepatic impairment (Child-Pugh B and C). No dose adjustment is required for mild, moderate or severe renal function; no safety or efficacy data is available for patients on hemodialysis.

Viekira Pak is classified as pregnancy category B, however, the regimen is classified as pregnancy category X when used in combination with ribavirin. Ribavirin is contraindicated in pregnant women and in men whose partners are pregnant. Animal studies that evaluated the components of Viekira Pak (ombitasvir, paritaprevir, ritonavir and dasabuvir) revealed no evidence of teratogenicity, however, adequate and well-controlled studies have not been conducted in pregnant women.

REFERENCES
• Fried M, Bisceglie A, Vierling J, Gane E, et al. Safety of ABT-450/r/ombitasvir plus dasabuvir with or without ribavirin in HCV genotype 1 infected patients: results from phase 2 and phase 3 trials.

<table>
<thead>
<tr>
<th>Library</th>
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