Medication Policy Manual

Policy No: dru387

Topic: Viekira Formulations

- Viekira Pak™, paritaprevir/ritonavir-ombitasvir plus dasabuvir
- Viekira XR™, dasabuvir-paritaprevir/ ritonavir-ombitasvir

Date of Origin: December 23, 2014

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Next Review Date: February 2018

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) and dasabuvir-paritaprevir/ ritonavir-ombitasvir (Viekira XR) are oral direct-acting antiviral combination regimens used for the treatment of chronic genotype 1 hepatitis C virus (HCV) infection.

Policy/Criteria

I. Most contracts require prior authorization approval of Viekira formulations (Viekira Pak, Viekira XR) prior to coverage. They may be considered medically necessary when criterion A, B, or C below is met.

CHRONIC HEPATITIS C GENOTYPE 1A

A. There is a diagnosis of chronic genotype 1a hepatitis C virus (HCV) infection and criteria 1 through 4 below are met:

1. Ribavirin will be used in combination with the Viekira formulation.

AND

2. There is documentation of the member's treatment history (see *Appendix 1*).

AND

3. There is clinical documentation indicating a medical reason why sofosbuvir-velpatasvir (Epclusa) AND ledipasvir-sofosbuvir (Harvoni) are not treatment options.

AND

4. Cycle Management Program requirements are met [refer to OmedaRx Medication Policy Manual, *Cycle Management Program*, dru404].

CHRONIC HEPATITIS C GENOTYPE 1B

B. There is a diagnosis of chronic genotype 1b hepatitis C virus (HCV) infection and criteria 1 through 3 below are met:

1. There is documentation of the member's treatment history (see *Appendix 1*).

AND

2. There is clinical documentation indicating a medical reason why sofosbuvir-velpatasvir (Epclusa) AND ledipasvir-sofosbuvir (Harvoni) are not treatment options.

AND

3. Cycle Management Program requirements are met [refer to OmedaRx Medication Policy Manual, *Cycle Management Program*, dru404].

POST-LIVER TRANSPLANT

C. There is a diagnosis of chronic hepatitis C virus (HCV) genotype 1 infection and criteria 1 through 5 below are met:

1. There is documentation that the member has received a liver transplant.

AND

2. Ribavirin will be used in combination with the Viekira formulation.

AND

3. There is documentation of the member's treatment history (see *Appendix 1*).

AND

4. There is clinical documentation indicating a medical reason why ledipasvir-sofosbuvir (Harvoni) is not a treatment option.

AND

5. Cycle Management Program requirements are met [refer to OmedaRx Medication Policy Manual, *Cycle Management Program*, dru404].

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers Viekira formulations (Viekira Pak, Viekira XR) to be self-administered medications.

B. When prior authorization is approved, Viekira formulations may be authorized in quantities as follows:

Patient Population [a]	Regimen	Quantity	Duration
Genotype 1a, without cirrhosis	Viekira + ribavirin	• **Viekira Pak**: Up to one monthly carton containing 28 daily dose packs per 28 days • **Viekira XR**: Up to 84 tablets per 28 days	12 weeks
Genotype 1a, with compensated cirrhosis	Viekira + ribavirin		24 weeks
Genotype 1b, with or without compensated cirrhosis	Viekira		12 weeks
Post-liver transplant	Viekira + ribavirin		24 weeks

[a] Including patients coinfected with HCV and HIV

III. Viekira formulations are considered investigational when used:

A. For durations beyond 24 weeks of treatment.

B. As retreatment when there has been relapse after, or no response to, a prior treatment course with a direct-acting antiviral for HCV (see *Appendix 2*).

C. In combination with any other direct-acting antiviral (see *Appendix 2*).

D. For all other conditions including, but not limited to:

1. Hepatitis C virus (HCV) genotypes other than genotype 1.
2. HCV infection in members with decompensated liver disease.
3. HCV in post-transplant patients with Metavir F3 or F4 scores.

Position Statement

- Paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) and dasabuvir-paritaprevir/ritonavir-ombitasvir (Viekira XR) are oral combinations of an NS5A inhibitor (ombitasvir), a NS3/4A protease inhibitor (paritaprevir), a non-nucleoside NS5B polymerase inhibitor (dasabuvir), and a medication that increases the overall drug exposure of paritaprevir (ritonavir). The combination of these medications with or without ribavirin is used for the treatment of chronic genotype 1 HCV infection in adults, including HCV/HIV coinfection and post-liver transplant patients.
- Viekira formulations have not been studied in patients previously treated with other oral direct-acting antivirals (DAAs). They have been shown to be safe and effective for treating chronic genotype 1 HCV infection in treatment-naïve patients and patients who were previously treated with peginterferon/ribavirin.
- The primary endpoint evaluated was the rate of viral cure, defined as a sustained virologic response (SVR) 12 weeks following the completion of therapy. Although SVR is measured by a series of HCV RNA levels and is considered a surrogate endpoint, it is accepted as a measure of efficacy for the treatment of HCV.
- Viekira formulations are packaged in a daily dose pack and is given for a total of 12 to 24 weeks of therapy based on the presence or absence of cirrhosis, HCV genotype 1 subtype, and if it is being used in the post-liver transplant setting.
- Ledipasvir-sofosbuvir (Harvoni) is another all oral, direct-acting antiviral used for the treatment of chronic genotype 1 HCV infection. Although not specifically FDA-approved in the post-transplant setting, the SOLAR-1 trial demonstrated high SVR rates in this high risk patient population. Ledipasvir-sofosbuvir (Harvoni) is the recommended regimen in AASLD/IDSA treatment guidelines for this population.
- Among all oral, direct-acting antivirals for chronic HCV genotype 1 infection, ledipasvir-sofosbuvir (Harvoni) provides the best value.

Clinical Efficacy

Treatment-Naïve Patients

Paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) has been shown to produce high viral cure rates in treatment-naïve patients with chronic genotype 1 hepatitis C virus (HCV) infection.

- One publication (which included two trials) evaluated paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak), with and without ribavirin, for 12 weeks in patients with HCV genotype 1a (PEARL-IV) or genotype 1b (PEARL-III). [1]
    * In genotype 1a patients, higher SVR12 rates were achieved in patients receiving concomitant ribavirin than those who did not (97.0% vs 90.2%, respectively).
    * In genotype 1b patients, SVR12 rates were similarly high among groups who did and did not receive concomitant ribavirin (99.5% vs 99.0%, respectively).
    * Virologic breakthrough and relapse occurred at a higher rate in genotype 1a patients compared to genotype 1b patients. Relapse occurred in > 5% of genotype 1 patients who did not receive concomitant ribavirin.

- A third published trial (SAPPHIRE-I) evaluated the efficacy of paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) with ribavirin versus placebo in patients with HCV genotype 1 without cirrhosis. [2]
    * SVR12 rates were consistently high among genotype 1a and genotype 1b patients (95.3% and 98.0%, respectively).
    * Virologic breakthrough and relapse occurred in < 2% of treated patients.
- A fourth published trial (TURQUOISE-II) evaluated the efficacy of paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) with ribavirin for 12 or 24 weeks in treatment-naïve HCV genotype 1 patients with compensated cirrhosis. [3]
    * In the subgroup of treatment-naïve patients, SVR rates were similar between 12 and 24 week treatment groups (94.2% and 94.6%, respectively).
- A fifth published trial (TURQUOISE-III) evaluated the efficacy of paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak without ribavirin in HCV genotype 1b patients. SVR12 rates were 100%. [4]

Treatment-Experienced Patients

Paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) has been shown to produce high viral cure rates in treatment-experienced patients with chronic genotype 1 hepatitis C virus (HCV) infection.

- A published trial (PEARL-II) evaluated the efficacy of paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak), with or without ribavirin, in previously treated patients with HCV genotype 1b who did not have cirrhosis. [5]
    * SVR12 rates were similarly high between patients who did and did not receive ribavirin (96.6% and 100%, respectively). SVR12 rates were numerically higher in prior null and partial responders who received ribavirin than those who did not (93.5% vs 100% and 96.0% vs 100%, respectively).
    * Virologic breakthrough and relapse were not reported in any patients.
- A second published trial (SAPPHIRE-II) evaluated the efficacy of paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) with ribavirin in previously treated HCV genotype 1 patients without cirrhosis. [6]
    * SVR12 rates were consistently high among prior relapsers, partial responders, and null responders (95.3%, 100% and 95.2%, respectively). The overall SVR rate reported was 96.3%.
    * Relapse was reported in 2.4% of treated patients, and no cases of virologic breakthrough were reported.
- A third published trial (TURQUOISE- II) evaluated the efficacy of paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) with ribavirin in previously treated HCV genotype 1 patients with compensated cirrhosis for 12 or 24 weeks. [3]

    * In the subgroup of treatment-experienced patients, SVR rates were similar between 12 and 24 week treatment groups in prior relapsers (96.6% vs 100%, respectively). SVR rates were numerically higher (> 5%) in prior partial and null responders who received 24 weeks of treatment instead of 12 weeks of treatment (100% vs 94.4% and 95.2% vs 86.7%, respectively).

- Recommendations for treatment experienced depend on individual patient characteristics which include: presence or absence of cirrhosis, HCV genotype 1 subtype, and previous HCV therapy.

HCV/HIV Coinfection

- A published trial (TURQUOISE-I) evaluated the efficacy of paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) with ribavirin in HCV/HIV coinfected patients stable on antiretroviral therapy for 12 or 24 weeks. [7]
    * All patients were on an antiretroviral regimen that included tenofovir disoproxil plus emtricitabine or lamivudine, administered with ritonavir-boosted atazanavir or raltegravir. The ritonavir component of the antiretroviral regimen was discontinued while patients were receiving paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) with ribavirin.
    * SVR12 was achieved in 91% of HCV genotype 1a and 100% of HCV genotype 1b patients. Of the five genotype 1a patients who did not respond to therapy, one experienced virologic breakthrough, one discontinued treatment, one experienced relapse, and two subjects were re-infected post-treatment.

Post-Liver Transplant

- A published trial (CORAL- I) evaluated the efficacy of paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) with ribavirin in HCV genotype 1 patients who had received a liver transplant for 24 weeks. [8]
    * All patients were on a stable tacrolimus- or cyclosporine-based immunosuppressive regimen and had received a liver transplant at least 12 months prior to entering the study. Enrolled patients could have received prior treatment for HCV with peginterferon and ribavirin, and had Metavir scores of F2 or lower.
    * The primary efficacy endpoint was the SVR rate at 12 weeks post-treatment. SVR was achieved in 33 of 34 patients (97%).

Clinical Guidelines

- As of October 2016, the Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) clinical guidelines recommend the following regimens for treatment-naïve patients with HCV. [9]

Genotype	Recommended Regimens		Alternative Regimens
Treatment-naïve patients			
1a	Without Cirrhosis	• Elbasvir-grazoprevir x 12 weeks (if no baseline NS5A RAVs) • Ledipasvir-sofosbuvir x 12 weeks • Viekira Pak + RBV x 12 weeks • Sofosbuvir + simeprevir x 12 weeks • Sofosbuvir-velpatasvir x 12 weeks • Daclatasvir + sofosbuvir x 12 weeks	Elbasvir-grazoprevir + RBV x 16 weeks (if baseline NS5A RAVs are present)
	Compensated Cirrhosis	• Elbasvir-grazoprevir x 12 weeks (if no baseline NS5A RAVs) • Ledipasvir-sofosbuvir x 12 weeks • Sofosbuvir-velpatasvir x 12 weeks	• Viekira Pak + RBV x 24 weeks • Simeprevir + sofosbuvir ± RBV x 24 weeks (if no Q80K polymorphism) • Daclatasvir + sofosbuvir ± RBV x 24 weeks • Elbasvir-grazoprevir + RBV x 16 weeks (if baseline NS5A RAVs are present)
1b	Without Cirrhosis	• Elbasvir-grazoprevir x 12 weeks • Ledipasvir-sofosbuvir x 12 weeks • Viekira Pak x 12 weeks • Sofosbuvir + simeprevir x 12 weeks • Sofosbuvir-velpatasvir x 12 weeks • Daclatasvir + sofosbuvir x 12 weeks	None listed
	Compensated Cirrhosis	• Elbasvir-grazoprevir x 12 weeks • Ledipasvir-sofosbuvir x 12 weeks • Viekira Pak x 12 weeks • Sofosbuvir-velpatasvir x 12 weeks	• Daclatasvir + sofosbuvir ± RBV x 24 weeks • Sofosbuvir + simeprevir ± RBV x 24 weeks
2	Without Cirrhosis	Sofosbuvir-velpatasvir x 12 weeks	Daclatasvir + sofosbuvir x 12 weeks
	Compensated Cirrhosis	Sofosbuvir-velpatasvir x 12 weeks	Daclatasvir + sofosbuvir x 16 to 24 weeks
3	Without Cirrhosis	• Daclatasvir + sofosbuvir x 12 weeks • Sofosbuvir-velpatasvir x 12 weeks	None listed
	Compensated Cirrhosis	• Sofosbuvir-velpatasvir x 12 weeks • Daclatasvir + sofosbuvir ± RBV x 24 weeks	None listed
4	Without Cirrhosis	• Technivie + RBV x 12 weeks • Sofosbuvir-velpatasvir x 12 weeks • Elbasvir-grazoprevir x 12 weeks • Ledipasvir-sofosbuvir x 12 weeks	None listed
	Compensated Cirrhosis	• Technivie + RBV x 12 weeks • Sofosbuvir-velpatasvir x 12 weeks • Elbasvir-grazoprevir x 12 weeks • Ledipasvir-sofosbuvir x 12 weeks	None listed
5 or 6	With or without Cirrhosis	• Sofosbuvir-velpatasvir x 12 weeks • Ledipasvir-sofosbuvir x 12 weeks	None listed

RBV = ribavirin; Technivie = ombitasvir, paritaprevir, and ritonavir; Viekira Pak = ombitasvir, paritaprevir, and ritonavir plus dasabuvir

- AASLD/IDSA guidelines state that patients with HCV/HIV coinfection should be treated similarly to non-coinfected patients; however, the potential for drug-drug interactions should be taken into consideration.

Safety

- In October 2015, the FDA released a drug safety communication stating the paritaprevir/ritonavir-ombitasvir (Technivie) and paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) may cause serious liver injury in patients with underlying advanced liver disease. Due to these warnings, AASLD/IDSA guidelines recommend close monitoring of total and direct bilirubin and transaminase levels every one week or two weeks for the first four weeks of therapy to ensure early detection of drug-induced liver injury. If monitoring cannot be provided during the first four weeks of therapy in patients with cirrhosis, the use of either regimen is not recommended. [10]
- The most commonly reported adverse events in clinical trial patients who received paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) with ribavirin (reported at an incidence ≥ 10%) include: fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. [11]
- The most commonly reported adverse events in clinical trial patients who received paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) without ribavirin (reported at an incidence ≥ 5%) include: nausea, pruritus, and insomnia. [11]

Dosing [11,12]

- The recommended dosing for paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak) is of two ombitasvir, paritaprevir, and ritonavir 12.5/75/50 mg tablets taken once daily in the morning and one dasabuvir 250 mg tablet taken twice daily with a meal.
- The recommended dosing for dasabuvir-paritaprevir/ritonavir-ombitasvir (Viekira XR) is three dasabuvir, ombitasvir, paritaprevir, and ritonavir 200/8.33/50/33.33 mg tablets taken once daily with a meal.
- The duration of therapy with paritaprevir/ritonavir-ombitasvir plus dasabuvir with or without ribavirin is dependent on the presence or absence of cirrhosis, HCV genotype 1 subtype, and medical history of a liver transplant.
    * Genotype 1a, without cirrhosis: paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak, Viekira XR) with ribavirin for 12 weeks.
    * Genotype 1a, with compensated cirrhosis: paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak, Viekira XR) with ribavirin for 24 weeks.
    * Genotype 1b, with or without cirrhosis: paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak, Viekira XR) for 12 weeks.
    * Post-liver transplant: paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak, Viekira XR) with ribavirin for 24 weeks.

Appendix 1: Definitions of Member Treatment History [9]	
Treatment-naive	Patients who have never received therapy for the treatment of hepatitis C.
Relapser	Patients who had an undetectable HCV RNA level at the end of prior therapy with peginterferon and ribavirin, but had a subsequent detectable HCV RNA level during the follow-up period.
Partial responder	Patients who had a HCV RNA reduction of ≥ 2 $\log_{10}$ after 12 weeks of prior therapy with peginterferon and ribavirin, but still had a detectable HCV RNA level during the treatment period.
Null responder	Patients who had a < 2 $\log_{10}$ reduction in HCV RNA after 12 weeks of prior therapy with peginterferon and ribavirin.

Appendix 2: Direct-acting Antivirals for HCV
boceprevir (Victrelis)
daclatasvir (Daklinza)
grazoprevir-elbasvir (Zepatier)
ledipasvir-sofosbuvir (Harvoni)
paritaprevir/ritonavir-ombitasvir (Technivie)
paritaprevir/ritonavir-ombitasvir plus dasabuvir (Viekira Pak, Viekira XR)
simeprevir (Olysio)
sofosbuvir (Sovaldi)
sofosbuvir-velpatasvir (Epclusa)
telaprevir (Incivek)

Cross References
Daklinza™, daclatasvir, dru411
Epclusa®, sofosbuvir-velpatasvir, dru457
Harvoni®, ledipasvir-sofosbuvir, dru366
Olysio®, simeprevir, dru331
Sovaldi®, sofosbuvir, dru332
Technivie™, paritaprevir/ritonavir-ombitasvir, dru412
Zepatier™, grazoprevir-elbasvir, dru435
Medical Policy Lab 47, Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease (http://blue.regence.com/trgmedpol/lab/lab47.pdf)

Codes	Number	Description
N/A		

References

1. Ferenci, P, Bernstein, D, Lalezari, J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med*. 2014 May 22;370(21):1983-92. PMID: 24795200
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 Apr 24;370(17):1594-603. PMID: 24720703
3. Poordad, F, Hezode, C, Trinh, R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med*. 2014 May 22;370(21):1973-82. PMID: 24725237
4. Feld, JJ, Moreno, C, Trinh, R, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12weeks. *J Hepatol*. 2016 Feb;64(2):301-7. PMID: 26476290
5. 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 Aug;147(2):359-65 e1. PMID: 24818763
6. 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 Apr 24;370(17):1604-14. PMID: 24720679
7. Sulkowski, MS, Eron, JJ, Wyles, D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA*. 2015;313:1223-31. PMID: 25706092
8. Kwo, PY, Mantry, PS, Coakley, E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med*. 2014 Dec 18;371(25):2375-82. PMID: 25386767
9. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C. October 2016a. [cited 01/22/2017]; Available from: http://hcvguidelines.org.
10. FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. [cited 1/18/2016]; Available from: http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm
11. Viekira Pak® [prescribing information]. North Chicago, IL: AbbVie, Inc.; June 2016
12. Viekira XR® [prescribing information]. North Chicago, IL: AbbVie, Inc.; July 2016

Revision History

Revision Date	Revision Summary
2/17/2017	• Removed requirement for concomitant ribavirin in genotype 1b with cirrhosis. • Removed coverage criteria for HCV with unknown genotype 1 subtype or mixed genotype 1 subtype.
11/11/2016	• Clarified inclusion in the Cycle Management Program, *dru404*.
7/22/2016	• Added Viekira XR to policy.
2/12/2016	• Removed requirement for advanced fibrosis, other end-organ disease manifestations, or other comorbid conditions. • Updated list of investigational uses.