PDL NEW DRUG REVIEW

Proprietary Name: Viekira® Pak
Common Name: ombitasvir, paritaprevir & ritonavir tabs; dasabuvir tabs
PDL Category: Hepatitis C Agents

Comparable Products	Preferred Drug List Status
Harvoni	Preferred with Conditions
Sovaldi	Preferred with Conditions

Summary

Indications and Usage: To be used with or without ribavirin for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis. Viekira® pak is not recommended for use in patients with decompensated liver disease. This is a pregnancy category B medication. The safety and efficacy of use in children have not been established.

Dosage Forms: Combination Tablets: 12.5mg/75mg/50mg, co-packaged with 250mg dasabuvir tablets

Recommended Dosage: Liver chemistry tests should be monitored before starting therapy, as well as during therapy. Take two ombitasvir/paritaprevir/ritonavir tabs QAM plus one dasabuvir tabs BID (QAM & QPM) with a meal without regard to fat or calorie content. In certain populations, Viekira® pak is used in combination with ribavirin. When used with Viekira®, the recommended ribavirin dose is 1000mg/day if <75kg or 1200mg/day if ≥75kg, divided and given BID with food. The following table, which was completely adapted from the PI, illustrates the treatment regimen and duration by patient population for treatment-naïve or interferon-experienced. The recommendations in the table below should also be followed for those who are HCV-HIV-1 co-infected.

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	Viekira® pak PLUS ribavirin	12 weeks
Genotype 1a, with cirrhosis	Viekira® pak PLUS ribavirin	24 weeks**
Genotype 1b, without cirrhosis	Viekira® pak	12 weeks
Genotype 1b, with cirrhosis	Viekira® pak PLUS ribavirin	12 weeks

*Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection

** Viekira® pak administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history

The recommended duration of Viekira® pak with ribavirin is 24 weeks in liver transplant recipients with normal hepatic function and mild fibrosis (metavir fibrosis score ≤2), regardless of HCV genotype 1 subtype. If Viekira® pak

is used concomitantly with calcineurin inhibitors in liver transplant recipients, dose adjustments of the calcineurin inhibitors are needed.

A significant list of DDIs has been established of certain drugs if given concomitantly with Viekira® pak. Please refer to the prescribing information for the effect on drug concentrations and the clinical comments.

Dose adjustments are not required in those with renal impairment or mild hepatic impairment; however, use is not recommended in those with moderate liver disease, is contraindicated in those with severe hepatic impairment, and has not been studied in those with dialysis.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Viekira® pak plus ribavirin) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than placebo.* The most frequently reported adverse events included fatigue (8%), nausea (7%), pruritus (11%), skin reactions (7%), insomnia (6%), and asthenia (7%). Reported lab abnormalities included serum ALT elevations, serum bilirubin elevations, and anemia/decreased hemoglobin.

Contraindications: If administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Please refer to the ribavirin prescribing information for a list of contraindications for ribavirin.

Viekira® pak is contraindicated with: drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, drugs that are strong inducers of CYP3A and CYP2C8 and may lead to reduced efficacy of Viekira® pak, and drugs that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation. The following list of drugs is contraindicated with Viekira® pak: alfuzosin, carbamazepine, phenytoin, phenobarbital, gemfibrozil, rifampin, ergot derivatives (ergotamine, dihydroergotamine, ergonovine, and methylergonovine), ethinyl estradiol-containing medications (such as combined oral contraceptives), St. John's Wort, lovastatin, simvastatin, pimozide, efavirenz, sildenafil when dosed as Revatio® for the treatment of PAH, triazolam, and orally administered midazolam.

Viekira® pak is also contraindicated in those with severe hepatic impairment and with known hypersensitivity to ritonavir.

Manufacturer: AbbVie

Analysis: Viekira® pak is a fixed dose combination tablet that contains a HCV NS5A inhibitor (ombitasvir), a HCV NS3/4A protease inhibitor (paritaprevir), and a potent CYP3A inhibitor (ritonavir) that is co-packaged with dasabuvir. Dasabuvir is a HCV non-nucleoside NS5B palm polymerase inhibitor. Ritonavir is not active against the HCV but rather increases the peak and trough drug concentrations of paritaprevir and overall drug exposure. Ombitasvir, paritaprevir, and dasabuvir are all considered direct-acting HCV antiviral agents.

The safety and efficacy of Viekira® pak was established in 6 randomized, multicenter studies. These studies are summarized in the table below, which was adapted from the PI.

Trial	Population	Study Arms (number of subjects treated)
SAPPHIRE-I * (double-blind)	GT1 (a & b) TN without cirrhosis	Viekira® pak + ribavirin X12W (N=473) VS placebo X12W* (N=158)
SAPPHIRE-II * (double-blind)	GT1 (a & b) TE without cirrhosis	Viekira® pak + ribavirin X12W (N=297) VS placebo X12W* (N=97)
PEARL-II (open-label)	GT1b TE without cirrhosis	Viekira® pak + ribavirin X12W (N=88) VS Viekira® pak X12W (N=91)
PEARL-III (double-blind)	GT1b TN without cirrhosis	Viekira® pak + ribavirin X12W (N=210) VS Viekira® pak X12W (N=209)

Trial	Population	Study Arms (number of subjects treated)
PEARL-IV (double-blind)	GT1a TN without cirrhosis	Viekira® pak + ribavirin X12W (N=100) VS Viekira® pak X12W (N=205)
TURQUOISE-II (open-label)	GT1 (a & b) TN & TE with cirrhosis	Viekira® pak + ribavirin X12W (N=208) VS Viekira® pak + ribavirin X24W (N=172)

GT1- genotype 1; TN- Treatment-naïve was defined as not having received any prior therapy for HCV infection

TE- Treatment-experienced subjects were defined as either: prior relapsers, prior partial responders, or prior null responders to peg INF/ribavirin treatment

*After the initial 12 weeks of treatment, the placebo arm received open-label Viekira® pak in combination with ribavirin for 12 weeks

Two additional studies assessed Viekira® pak in specific populations, and they include HCV GT1-infected liver transplant recipients (CORAL-1) and subjects with HCV GT1 co-infected with HIV-1 (TURQUOISE-1).

***SAPPHIRE-1*[2]:** The SVR rate of Viekira® pak plus ribavirin at week 12 was non-inferior and superior to the historical control rate that was telaprevir with peginterferon/ribavirin.

Outcome	Viekira® pak + ribavirin	Placebo
SVR rate at week 12 (all patients)	96.2%	78% (Historical control)
SVR G1a	95.3%	72% (Historical control)
SVR G1b	98%	80% (Historical control)
Virologic failure during treatment	0.2%	
Relapse after treatment	1.5%	
Rate of discontinuation due to adverse events	0.6%	0.6%

Historical control with telaprevir + peginterferon-ribavirin

PEARL-II*[3]*: The SVR rate at week 12 in both groups was non-inferior and superior to the historical control group of telaprevir plus peg-interferon/ribavirin. The rate of response in the Viekira® pak group was non-inferior to that of the Viekira® pak plus ribavirin group.

Outcome	Viekira® pak + ribavirin	Viekira® pak
SVR rate at week 12 (all patients)	96.6%	100%
Virologic failure during treatment	0%	0%
Relapse after treatment	0%	0%
Rate of discontinuation due to adverse events	1.1%	0%

TURQUOISE-II* [4]*: The SVR rate for each of the treatment groups was non-inferior and superior to the historical control rate with telaprevir plus peg-interferon/ribavirin. Differences between the two Viekira® treatment groups below were not significant (p=0.09). Significantly more in the 12 week group had relapse vs the 24 week group.

Outcome	Viekira® pak + ribavirin X12W	Viekira® pak + ribavirin X24W
SVR rate at week 12 (all patients)	91.8%	95.9%
SVR G1a	88.6%	94.2%
SVR G1b	98.5%	100%
Virologic failure during treatment	0.5%	1.7%
Relapse after treatment	5.9%	0.6%
Rate of discontinuation due to adverse events	2%	2%

PEARL III and PEARL IV*[5]*: *PEARL IV*: The SVR rates for the Viekira® groups with and without ribavirin were both non-inferior and superior to the historical control with telaprevir plus peginterferon-ribavirin in adults with G1a. The group without ribavirin did not meet non-inferiority criteria vs the group with ribavirin. In addition, there was a significant difference between groups. *PEARL III*: The SVR rates in the Viekira® groups with or without ribavirin were both non-inferior and superior to the historical control rate with telaprevir plus peginterferon-ribavirin in adults with G1b. The SVR rate with those not receiving ribavirin was non-inferior to the rate of those receiving ribavirin.

Outcome	Viekira® pak + ribavirin X12W	Viekira® pak without ribavirin
Genotype 1a		
SVR rate	97% (vs 72% historical control)	90.2%
Virologic failure during treatment	1%	2.9%
Relapse	1%	5.2%
Discontinuations due to adverse events	0.3%	
Genotype 1b		
SVR rate	99.5% (vs 80% historical control)	99%
Virologic failure during treatment	0.5%	0%
Relapse	0%	0%
Discontinuations due to adverse events	0%	0%

SAPPHIRE-II*[6]*: The overall SVR rate for Viekira® pak plus ribavirin was non-inferior and superior to the historical control rate with telaprevir plus peginterferon/ribavirin.

Outcome	Viekira® pak + ribavirin	Placebo
SVR rate at week 12 (all patients)[1]	96.3%	65% (Historical control)
SVR G1a	96%	
SVR G1b	96.7%	

Outcome	Viekira® pak + ribavirin	Placebo
Virologic failure during treatment	0%	
Relapse	2.4%	
Discontinuation due to adverse events	1%	0%

[1] Rates were: 95.3% among those with a prior relapse, 100% among those with a prior partial response, and 95.2% among those with a prior mull response.

CORAL-I[1]: This was a small 24-week study (N=34) that included HCV genotype 1-infected liver transplant recipients who were ≥12 months post transplantation with normal hepatic function and mild fibrosis. All were treated with Viekira® pak with ribavirin. The SVR rate at week 12 was 97%, and specifically 97% of subjects with G1a and 100% of subjects with G1b. There was one relapse post-treatment who was G1a.

TURQUOIS-I[1]: This small open-label study (N=63) included subjects with HCV genotype1 infection co-infected with HIV-1 who were treated for 12 or 24 weeks with Viekira® pak in combination with ribavirin. Subjects were on a stable HIV-1 antiretroviral therapy (ART) regimen. The SVR rate at week 12 was 91% for those with G1a (N=51/56) and 100% for those with G1b (N=7/7). There were 5 non-responders that included 1 with virologic breakthrough, 1 who discontinued treatment, 1 with relapse, and 2 with evidence of HCV re-infection post-treatment.

The studies discussed above do suggest potent antiviral activity in a population with HCV genotype 1 based on significantly high SVR rates. Superiority was based on historical control rates. In addition, treatment discontinuations due to adverse events were low to absent. Determination of the clinically optimal and most cost-effective regimen for Hepatitis C is complex and it is recommended that this drug be preferred but require prior authorization to determine specific clinical conditions in order to ensure appropriate use.

PDL Placement:

- ☐ **Preferred**
- ☐ **Non-Preferred**
- ☒ **Preferred with Conditions**

References

[1] Viekira pak [package insert]. North Chicago, IL: AbbVie Inc; 2014.
[2] Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *NEJM.* 2014; 370(17): 1594-603.
[3] Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavior, 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(2): 359-365.
[4] Poordad F, Hezode C, Trinh r, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitic C with cirrhosis. *NEJM*. 2014; 370(21): 1973-82.
[5] Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *NEJM*. 2014; 370(21): 1983-92.
[6] Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavin. *NEJM*. 2014; 370(17): 1604-14.