

VIEKIRA PAK[®] (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use
Medicaid Clinical Summary
December 2014

BACKGROUND

- Chronic hepatitis C (HCV) is a serious viral infection that can result in liver damage or hepatocellular carcinoma in some patients.
- The prevalence of chronic HCV infection in the United States is estimated to be 2.2 to 3.2 million in the non-institutionalized, civilian population with up to 75% of those individuals unaware of their infection status.² The majority of patients in the United States are infected with HCV genotype 1 (76%).³
- The prevalence of decompensated cirrhosis and hepatocellular carcinoma from advanced HCV disease are projected to increase through approximately 2020 in the United States, assuming no increase in the current treatment rates.⁴
- In addition to the hepatic manifestations of chronic HCV infection (liver damage, cirrhosis, hepatocellular carcinoma), approximately 75% of patients will develop extra-hepatic manifestations such as fibromyalgia, systemic lupus erythematosus, pruritus, cryoglobulinemic vasculitis, non-Hodgkin's lymphoma, and multiple myeloma during their illness.⁵ Chronic HCV infection is also associated with numerous comorbid conditions including type 2 diabetes, psychiatric conditions, HIV co-infection, and end-stage renal disease.⁶⁻⁸
- The American Association for the Study of Liver Diseases (AASLD)/Infectious Disease Society of America (IDSA)/International Antiviral Society-USA (IAS-USA) Recommendations for Testing, Managing, and Treating Hepatitis C recommends that highest priority be given to treating patients with chronic HCV infections with advanced hepatic fibrosis (METAVIR F3) or compensated cirrhosis (METAVIR F4), organ transplant, or the extra-hepatic manifestations of type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (e.g., vasculitis), proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis. The guidelines also recommend that high priority be given to the treatment of patients with chronic HCV infections and hepatic fibrosis (METAVIR F2), HIV coinfection, HBV coinfection, other coexisting liver disease (e.g., nonalcoholic steatohepatitis [NASH]), debilitating fatigue, type 2 diabetes mellitus, or porphyria cutanea tarda.⁹
- In the United States, deaths due to hepatitis C virus have surpassed HIV in recent years.¹⁰
- Successful HCV treatment results in sustained virologic response (SVR), which is equivalent to virologic cure; virologic cure is expected to benefit chronically infected persons.¹¹

INDICATIONS AND USAGE

VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

Limitation of Use:

VIEKIRA PAK is not recommended for use in patients with decompensated liver disease.

MECHANISM OF ACTION

- 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 polymerase inhibitor.

CONTRAINDICATIONS

- If VIEKIRA PAK 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.
- If VIEKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- VIEKIRA PAK is contraindicated in patients with severe hepatic impairment due to risk of potential toxicity.
- VIEKIRA PAK is contraindicated in patients with known hypersensitivity (e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir.
- 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.
 - Drugs that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation.
- The safety and efficacy of VIEKIRA PAK has not been established in patients with HCV genotypes other than genotype 1.

DOSAGE AND ADMINISTRATION

- The recommended oral dose of VIEKIRA PAK is 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.
- The treatment duration for most genotype 1 patient populations is 12 weeks, including HCV/HIV-1 co-infection patients. The treatment duration for genotype 1a patients with cirrhosis is 24 weeks, although VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history. Additionally, 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.

WARNINGS AND PRECAUTIONS

- During clinical trials with VIEKIRA PAK with or without ribavirin, elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects. ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment, and declined within two to eight weeks of onset with continued dosing of VIEKIRA PAK with or without ribavirin.
- These ALT elevations were significantly more frequent in female subjects who were using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches or contraceptive vaginal rings. Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with VIEKIRA PAK. Alternative methods of contraception (e.g., progestin only contraception or non-hormonal methods) are recommended during VIEKIRA PAK therapy. Ethinyl estradiol-containing medications can be restarted

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approximately 2 weeks following completion of treatment with VIEKIRA PAK.

- Women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with VIEKIRA PAK
- If VIEKIRA PAK is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.
- VIEKIRA PAK is not recommended in HCV-infected patients with moderate hepatic impairment (Child-Pugh B). VIEKIRA PAK is contraindicated in patients with severe (Child-Pugh C) hepatic impairment
- Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter.
- The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of VIEKIRA PAK and possible development of resistance or possible clinically significant adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK. Consult the full prescribing information prior to use for potential drug-drug interactions.
- The ritonavir component of VIEKIRA PAK is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with VIEKIRA PAK should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

KEY CLINICAL TRIAL SUMMARY

- The efficacy and safety of VIEKIRA PAK was evaluated in six randomized, multicenter, clinical trials in 2,308 subjects with genotype 1 (GT1) chronic hepatitis C virus (HCV) infection, including one trial exclusively in subjects with cirrhosis with mild hepatic impairment (Child-Pugh A)

Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection without Cirrhosis

- SVR₁₂ rate of 96% was seen in GT1a treatment-naïve subjects without cirrhosis treated with VIEKIRA PAK in combination with ribavirin in the placebo-controlled trial, SAPPHERE-I (GT1a treatment-naïve, n=322) and an SVR₁₂ rate of 97% was seen in GT1a treatment-naïve subjects without cirrhosis receiving ribavirin in PEARL-IV (GT1a treatment-naïve, n=100) for 422 GT1a subjects without cirrhosis treated with VIEKIRA PAK in combination with ribavirin. SVR₁₂ rate of 96% was seen in GT1a treatment-experienced subjects in the placebo-controlled trial, SAPPHERE-II (GT1a treatment-experienced, n=173). In SAPPHERE-I and SAPPHERE-II, no placebo subject achieved a HCV RNA <25 IU/mL during treatment.
- Treatment-naïve, HCV GT1a-infected subjects without cirrhosis treated with VIEKIRA PAK in combination with ribavirin for 12 weeks in PEARL-IV had a significantly higher SVR₁₂ rate than subjects treated with VIEKIRA PAK alone (97% and 90% respectively; difference +7% with 95% confidence interval, +1% to +12%). VIEKIRA PAK alone was not studied in treatment-experienced subjects with GT1a infection.
- The SVR rate for HCV GT1b-infected subjects without cirrhosis treated with VIEKIRA PAK without ribavirin for 12 weeks in PEARL-II (treatment-experienced: null responder, n=32; partial responder, n=26; relapser, n=33) and PEARL-III (treatment-naïve, n=209) was 100%.

Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection and Compensated Cirrhosis

- TURQUOISE-II was an open-label trial that enrolled 380 HCV GT1a and 1b-infected subjects with cirrhosis and mild hepatic impairment (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegylated interferon (pegIFN)/ribavirin.
- SVR₁₂ rate of 95% was seen in GT1a subjects treated with VIEKIRA PAK with ribavirin for 24 weeks in TURQUOISE II.
- In GT1a infected subjects, the overall SVR₁₂ rate difference between 24 and 12 weeks of treatment with VIEKIRA PAK with ribavirin was +6% with 95% confidence interval, -0.1% to +13% with differences varying by pretreatment history.
- SVR₁₂ rates of 99% were seen in Genotype 1b-infected subjects when treated with VIEKIRA PAK plus ribavirin for 12 weeks.

Effect of Ribavirin Dose Reductions on SVR₁₂

- Seven percent of subjects (101/1551) treated with VIEKIRA PAK with ribavirin had a ribavirin dose adjustment due to a decrease in hemoglobin level; of these, 98% (98/100) achieved an SVR₁₂.

Clinical Trial of Selected Liver Transplant Recipients (CORAL-I)

- Of the 34 subjects (29 with HCV GT1a infection and 5 with HCV GT1b infection) enrolled, (97%) achieved SVR₁₂ (97% in subjects with GT1a infection and 100% of subjects with GT1b infection). One subject with HCV GT1a infection relapsed post-treatment.

Clinical Trial in Subjects with HCV/HIV-1 Co-infection (TURQUOISE-I)

- In an open-label clinical trial 63 subjects with HCV GT1 infection co-infected with HIV-1 (19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/ ribavirin; 89% of subjects had HCV genotype 1a infection) were treated for 12 or 24 weeks with VIEKIRA PAK in combination with ribavirin.
- The SVR₁₂ rates were 91% (51/56) for subjects with HCV GT1a infection and 100% (7/7) for those with HCV GT1b infection.

Durability of Response

- In an open-label clinical trial, 92% of subjects (526/571) who received various combinations of the direct acting antivirals included in VIEKIRA PAK with or without ribavirin achieved SVR₁₂, and 99% of those who achieved SVR₁₂ maintained their response through 48 weeks post-treatment (SVR₄₈).

IMPORTANT SAFETY INFORMATION

- The safety assessment was based on data from six Phase 3 clinical trials in more than 2,000 subjects who received VIEKIRA PAK with or without ribavirin for 12 or 24 weeks.
- The safety of VIEKIRA PAK in combination with ribavirin was assessed in 770 subjects with chronic HCV infection in two placebo-controlled trials (SAPPHERE-I and -II). Adverse reactions that occurred more often in subjects treated with VIEKIRA PAK in combination with ribavirin compared to placebo were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. The

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majority of the adverse reactions were mild in severity. Two percent of subjects experienced a serious adverse event (SAE). The proportion of subjects who permanently discontinued treatment due to adverse reactions was less than 1%.

- VIEKIRA PAK with and without ribavirin was assessed in 401 and 509 subjects with chronic HCV infection, respectively, in three clinical trials (PEARL-II, PEARL-III and PEARL-IV). Pruritus, nausea, insomnia, and asthenia were identified as adverse events occurring more often in subjects treated with VIEKIRA PAK in combination with ribavirin. The majority of adverse events were mild to moderate in severity. The proportion of subjects who permanently discontinued treatment due to adverse events was less than 1% for both VIEKIRA PAK in combination with ribavirin and VIEKIRA PAK alone.
- VIEKIRA PAK with ribavirin was assessed in 380 subjects with compensated cirrhosis who were treated for 12 (n=208) or 24 (n=172) weeks duration (TURQUOISE-II). The type and severity of adverse events in subjects with compensated cirrhosis was comparable to non-cirrhotic subjects in other phase 3 trials. Fatigue, skin reactions and dyspnea occurred at least 5% more often in subjects treated for 24 weeks. The majority of adverse events occurred during the first 12 weeks of dosing in both treatment arms. Most of the adverse events were mild to moderate in severity. The proportion of subjects treated with VIEKIRA PAK for 12 and 24 weeks with SAEs was 6% and 5%, respectively and 2% of subjects permanently discontinued treatment due to adverse events in each treatment arm.
- VIEKIRA PAK with ribavirin was assessed in 63 subjects with HCV/HIV-1 co-infection who were on stable antiretroviral therapy. The most common adverse events occurring in at least 10% of subjects were 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%) subjects. Fifteen of these subjects were also receiving atazanavir at the time of bilirubin elevation and nine also had adverse events of ocular icterus, jaundice or hyperbilirubinemia. None of the subjects with hyperbilirubinemia had concomitant elevations of aminotransferases. No subject experienced a grade 3 ALT elevation. Seven subjects (11%) had at least one post-baseline hemoglobin value of less than 10 g/dL, and six of these subjects had a ribavirin dose modification; no subject in this small cohort required a blood transfusion or erythropoietin. Median declines in CD4+ T-cell counts of 47 cells/mm³ and 62 cells/mm³ 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+ T-cell counts decrease to less than 200 cells/mm³ during treatment without a decrease in CD4%. No subject experienced an AIDS-related opportunistic infection.
- VIEKIRA PAK with ribavirin was assessed in 34 post-liver transplant subjects with recurrent HCV infection. Adverse events occurring in more than 20% of subjects 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.

Please see full prescribing information, available at www.rxabbvie.com.

REFERENCES

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