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Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir *(Viekira Pak)*

Discontinued. This treatment has been discontinued.

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Drug Summary

The all-oral regimen ombitasvir-paritaprevir-ritonavir and dasabuvir, with or without ribavirin, provides another option for patients with chronic HCV genotype 1a infection (without cirrhosis or with compensated cirrhosis when given with ribavirin) and genotype 1b (without cirrhosis or with compensated cirrhosis). Overall, this combination regimen appears to be well tolerated, but severe hepatotoxicity associated with hepatic decompensation and death were reported post-marketing, mainly in patients with moderate-to-severe hepatic impairment (Child-Pugh B and C). The potential risk of severe liver complications in some patients underscores the importance of staging patients prior to treatment to identify any with moderate-to-severe hepatic impairment. This regimen is dosed twice daily and requires a higher pill burden than some other direct-acting antiviral options, particularly when ribavirin is included. Like elbasvir-grazoprevir, this combination has been shown to be safe and effective in patients with advanced kidney disease

Adverse Effects

On October 22, 2015 the United States FDA issued a Drug Safety Warning that treatment with ombitasvir-

paritaprevir-ritonavir and dasabuvir (*Viekira Pak*) can cause serious liver injury, mostly in patients with underlying advanced liver disease. In most of the reported cases, the liver injury occurred within 1 to 4 weeks of starting treatment. Available data from clinical trials have demonstrated excellent tolerance with the ombitasvir-paritaprevir-ritonavir and dasabuvir regimen. The most common (greater than 10%) adverse effects observed in clinical trials when used without ribavirin have been fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. The concomitant use of ombitasvir-paritaprevir-ritonavir and dasabuvir with ethinyl estradiol-containing medications can result in significant elevations in hepatic aminotransferase levels; accordingly patients should discontinue any ethinyl estradiol-containing medications prior to starting ombitasvir-paritaprevir-ritonavir and dasabuvir. Ribavirin can cause significant adverse effects, including hemolytic anemia. Further, ribavirin is highly teratogenic and embryocidal, and extreme care must be given to avoid pregnancy during therapy and for 6 months after completing therapy; this pertains both to treatment of women receiving ribavirin treatment and women whose male partners are receiving ribavirin therapy. Consult the ribavirin prescribing information for detailed information on ribavirin-related adverse effects and precautions for use of ribavirin.

Class and Mechanism

The *Viekira Pak* is an all-oral regimen comprised of four medications: ombitasvir, paritaprevir, ritonavir, and dasabuvir. This regimen can be used with or without ribavirin. In the *Viekira Pak*, the ombitasvir-paritaprevir-ritonavir are combined as a fixed-dose tablet and the dasabuvir is a separate tablet. Ombitasvir is a NS5A inhibitor with potent pangenotypic picomolar antiviral activity, paritaprevir is an inhibitor of the NS3/4A serine protease, and dasabuvir is a nonnucleoside NS5B polymerase inhibitor. Ritonavir is a potent inhibitor of CYP3A4 enzymes and is used as a pharmacologic booster for paritaprevir—it significantly increases peak and trough paritaprevir plasma concentrations, as well as the area under the curve of paritaprevir. Ritonavir was originally developed and FDA-approved as an HIV protease inhibitor; it does not have activity against HCV.

Manufacturer for United States

The *Viekira Pak* (vee-KEE-rah-pak) contains the fixed-dose combination of ombitasvir-paritaprevir-ritonavir plus dasabuvir) (Figure 1) and (Figure 2). It is manufactured by AbbVie. The drug paritaprevir was discovered and developed as part of a collaborative effort between AbbVie and Enanta Pharmaceuticals. Ribavirin, which is recommended for use with the *Viekira Pak* in specific patient populations, is manufactured by multiple companies in the United States and is available in generic formulations.

FDA Status

On December 19, 2014, the United States FDA approved ombitasvir-paritaprevir-ritonavir and dasabuvir for the treatment of genotype 1 chronic hepatitis C infection in adults, including patients with compensated cirrhosis. The medications ombitasvir, paritaprevir, and dasabuvir do not have FDA approval for use as individual drugs outside of use in the *Viekira Pak*. The drug ritonavir was previously approved by the FDA for use as an HIV protease inhibitor.

Indications

The regimen ombitasvir-paritaprevir-ritonavir plus dasabuvir is FDA-approved for the treatment of chronic hepatitis C genotype 1, including those with compensated cirrhosis. The recommendations for use of the *Viekira Pak* refer to a dosing regimen of 2 tablets once daily of the fixed-dose combination ombitasvir-paritaprevir-ritonavir plus one tablet twice daily of dasabuvir. The regimen ombitasvir-paritaprevir-ritonavir plus dasabuvir is approved for use in both treatment-naive and treatment-experienced patients. The treatment duration and inclusion of ribavirin depends on the genotype 1 subtype and the presence or absence of cirrhosis; ribavirin is recommended with all regimens except for Genotype 1b without cirrhosis (Figure 2).

- Genotype 1a, without cirrhosis: ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin for 12 weeks
- Genotype 1a, with cirrhosis: ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin for 24 weeks NOTE: a duration of 12 weeks may be considered for some patients based on prior treatment history. In the Turquoise-II study, patients with genotype 1a, cirrhosis, and prior treatment failure with peginterferon and ribavirin received either a 12- or 24-week treatment course of ombitasvir-paritaprevir-ritonavir plus dasabuvir plus ribavirin. The SVR12 rates in the 12- and 24-week groups were similar for prior relapsers and partial responders, but prior genotype 1a null responders had significantly lower SVR12 responses when treated with 12 weeks than with 24 weeks (80% versus 93%).
- Genotype 1b, without cirrhosis: ombitasvir-paritaprevir-ritonavir and dasabuvir for 12 weeks
- Genotype 1b, with cirrhosis: ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin for 12 weeks
- For patients with unknown genotype 1 subtype or mixed genotype 1 infection, use the regimen and duration as recommended for genotype 1a.
- For patients with HIV coinfection, use the same dosage recommendations as listed above.
- For liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score less than or equal to 2), the recommended treatment is ombitasvir-paritaprevir-ritonavir plus dasabuvir plus ribavirin for a duration of 24 weeks.
- Treatment with ombitasvir-paritaprevir-ritonavir and dasabuvir is contraindicated in the following circumstances: (1) patients with hepatic decompensation, (2) patients receiving medications highly dependent on CYP3A for clearance for which significant increases in plasma levels may result in life-threatening events, (3) patients receiving strong inducers of CYP3A or CYP2C8, which may lead to reduced efficacy for hepatitis C treatment, (4) patients receiving strong inhibitors of CYP2C8 since this may cause increases in dasabuvir levels and QT prolongation, or (5) known hypersensitivity to ritonavir.

Contraindications

Ombitasvir-paritaprevir-ritonavir and dasabuvir is contraindicated in following situations:

- Patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to the risk of hepatoxicity.
- With coadministration of drugs that are highly dependent on CYP3A for clearance for which elevated plasma levels could lead to serious toxicity.
- With coadministration of moderate or strong inducers of CYP3A and strong inducers of CYP2C8 since these medications may lead to reduced efficacy of ombitasvir-paritaprevir-ritonavir and dasabuvir.
- With coadministration of medications that are strong inhibitors of CYP2C8 since these medications may increase dasabuvir levels and cause QT prolongation.
- In patients who have known hypersensitivity to the medication ritonavir.

- If ribavirin is used in combination with ombitasvir-paritaprevir-ritonavir, the contraindications to ribavirin apply to the treatment regimen.

Note: see the prescribing information for a list of medications contraindicated for use with ombitasvir-paritaprevir-ritonavir and dasabuvir.

Dosing

The daily *Viekira Pak* container contains two tablets of the co-formulated ombitasvir-paritaprevir-ritonavir (12.5/75/50 mg) and two tablets of dasabuvir (250 mg) (Figure 3). The weekly dose carton has 7 of the daily *Viekira Pak* containers.

- Recommended Dosing: Two tablets of the co-formulated ombitasvir-paritaprevir-ritonavir (12.5/75/50 mg) once daily plus one dasabuvir tablet (250 mg) twice daily, with food, but without regard to fat or calorie content.
- Ribavirin Dosing: If ribavirin is administered with this regimen, the dosing should be weight based and divided twice daily (total daily dose of 1000 mg if less than or equal to 75 kg and 1200 mg if greater than 75 kg).
- Dosing with Renal Impairment: For patients with mild, moderate, or severe renal insufficiency, no dosing adjustment is required for the regimen ombitasvir-paritaprevir-ritonavir and dasabuvir; this regimen, however, has not been adequately studied in patients with end-stage renal disease on dialysis. The recommendations for the use of ribavirin in patients with renal impairment are controversial; therefore, the clinician should refer to the specific ribavirin prescribing information and obtain expert consultation.
- Dosing with Hepatic Impairment: For patients with mild hepatic impairment (Child-Pugh A), no dosage adjustment is required for ombitasvir-paritaprevir-ritonavir and dasabuvir; this regimen is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated with severe hepatic impairment (Child-Pugh C).

Clinical Use

The regimen ombitasvir-paritaprevir-ritonavir plus dasabuvir, with or without ribavirin, has primarily been studied as an all-oral (interferon-free) regimen in treatment-naive and treatment-experienced patients with genotype 1a or 1b chronic HCV infection, including those with compensated cirrhosis, HIV coinfection, and after receipt of liver transplantation. Six major studies that have involved a total of 2308 patients with genotype 1 infection have shown SVR12 rates of approximately 91 to 100% using ombitasvir-paritaprevir-ritonavir plus dasabuvir, with or without ribavirin. This regimen can be used in patients coinfected with HIV and in post-transplantation patients with a Metavir fibrosis score of 2 or less.

Cost and Medication Access

The wholesale acquisition cost (WAC) for a 12-week treatment course with *Viekira Pak* is $83,319. The cost for a 24-treatment course with the *Viekira Pak* is $166,638. The exact added cost of ribavirin, if used, is more difficult to determine because of variable daily doses when using the recommended weight-based dosing and

the availability of ribavirin through multiple companies. Roughly, the cost of a 12-week treatment with generic ribavirin is roughly $700 and for 24 weeks it is $1400.

The AbbVie patient assistance program (proCeed) offers a broad range of patient support and financial information. The program can also be accessed at the proCeed page on the Viekira Pak web site or by calling 1-844-2-PROCEED (1-844-277-6233).

Resistance

In a pooled analysis of more than 2,000 subjects who were treated with ombitasvir, paritaprevir, ritonavir, and dasabuvir, with or without ribavirin in the phase 2b and 3 trials, 64 patients with genotype 1 infection who experienced virologic failure were evaluated for treatment-emergent resistance. Among those 64 patients, 20 had on-treatment virologic failure and 44 has post-treatment relapse. Treatment-emergent mutations were observed in all the three major drug targets (NS3, NS5a, and NS5B) in 30 (53%) of 57 patients with genotype 1a infection and in 1 (17%) of 6 patients genotype 1b. Among the 58 patients with genotype 1a, 88% developed a NS3 mutation, 78% NS5A mutation, and 67% an NS5B mutation. The efficacy ofombitasvir-paritaprevir-ritonavir plus dasabuvir is not known for patients with prior virologic failure and resistance with treatment that included another NS3/4A inhibitor, NS5A inhibitor, or NS5B inhibitor. In addition, for patients who develop virologic failure and resistance when treated with ombitasvir-paritaprevir-ritonavir plus dasabuvir, the impact on subsequent therapy with other NS3/4A, NS5A, or NS5B inhibitors remains unknown. The medication ritonavir, which is used as a pharmacologic booster, has activity against HIV protease; accordingly any patient with HIV coinfection should have full suppression of HIV RNA levels prior to and during receipt of ombitasvir-paritaprevir-ritonavir and dasabuvir.

Key Drug Interactions

For complete information on ombitasvir-paritaprevir-ritonavir and dasabuvir-related drug interactions, see the Drug Interactions section in the Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (*Viekira Pak*) Prescribing Information.

Full Prescribing Information

Ombitasvir-paritaprevir-ritonavir plus dasabuvir (*Viekira Pak*) Full Prescribing information for use in the United States.

Figures

Figure 1. Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (*Viekira Pak*) Daily Treatment

Figure 2. Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (*Viekira Pak*) Weekly Dose Carton

Figure 3. Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir: Indications and Usage

Note all regimens include ribavirin except for genotype 1b without cirrhosis.

Source: *Viekira Pak* Prescribing Information, AbbVie Inc.

Figure 4. Drugs Contraindicated for Use with Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir

See the full prescribing information for a more detailed description, including the specific complication that may result from these drug-drug interactions

Modified from *Viekira Pak* Prescribing Information, AbbVie Inc.

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