



Grazoprevir/Elbasvir (Zepatier™) New Drug Update

February 2016

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| Drug Name: | grazoprevir/elbasvir |
| Trade Name (Manufacturer): | Zepatier (Merck) |
| Form: | Tablet |
| Strength: | 50 mg elbasvir and 100 mg grazoprevir |
| FDA Approval: | January 28, 2016 |
| Market Availability: | Currently Available |
| FDA Approval Classification: | Priority Review; Breakthrough Therapy |
| Classification: | Specific Therapeutic Class (HIC3): Hepatitis C Virus – NS5A Replication Complex Inhibitors (WOA) |

INDICATION¹

Grazoprevir/elbasvir (Zepatier), a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor, is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults.

CONTRAINDICATIONS/WARNINGS¹

Grazoprevir/elbasvir is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C), and in patients who are taking a concomitant OATP1B1/3 inhibitors, strong CYP3A inducers, or efavirenz.

If grazoprevir/elbasvir is administered with ribavirin, the contraindications to ribavirin also apply. Ribavirin is contraindicated in pregnant women and men whose female partners are pregnant, patients with hemoglobinopathies, and patients receiving coadministration with didanosine.

During clinical trials with grazoprevir/elbasvir with or without ribavirin, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN). Hepatic laboratory testing needs to be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing needs to be performed at treatment week 12. For ALT elevations on grazoprevir/elbasvir, discontinuation of the drug should be considered if the elevation is greater than 10 times the ULN or if the ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

If grazoprevir/elbasvir is administered with ribavirin, the warnings and precautions for ribavirin, including the pregnancy avoidance warning, also apply to this combination regimen.

| Drug Class | Drug(s) within Class that are Contraindicated | Clinical Comment* |
|--------------------|--|---|
| Anticonvulsants | Phenytoin Carbamazepine | May lead to loss of virologic response to grazoprevir/elbasvir due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction. |
| Antimycobacterials | Rifampin | May lead to loss of virologic response to grazoprevir/elbasvir due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction |
| Herbal Products | St. John's Wort (Hypericum perforatum) | May lead to loss of virologic response to grazoprevir/elbasvir due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction. |
| HIV Medications | Efavirenz | May lead to loss of virologic response to grazoprevir/elbasvir due to significant decreases in elbasvir and grazoprevir plasma |
| HIV Medications | Atazanavir Darunavir Lopinavir Saquinavir Tipranavir | May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition. |
| Immunosuppressants | Cyclosporine | May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition. |

*This table is not a comprehensive list of all drugs that inhibit OATP1B1/3 or strongly induce CYP3A

DRUG INTERACTIONS¹

Grazoprevir is a substrate of OATP1B1/3 transporters. Co-administration of grazoprevir/elbasvir with drugs that inhibit OATP1B1/3 transporters may result in a significant increase in the plasma concentrations of grazoprevir. As such, co-administration of grazoprevir/elbasvir with OATP1B1/3 inhibitors is contraindicated. Elbasvir and grazoprevir are substrates of CYP3A and P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir appears to be minimal. Co-administration of moderate or strong inducers of CYP3A with grazoprevir/elbasvir may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of grazoprevir/elbasvir. Co-administration of grazoprevir/elbasvir with strong CYP3A inducers or efavirenz is contraindicated. Co-administration of grazoprevir/elbasvir with moderate CYP3A inducers is not recommended. Co-administration of grazoprevir/elbasvir with strong CYP3A inhibitors may increase elbasvir and grazoprevir concentrations. Co-administration of grazoprevir/elbasvir with certain strong CYP3A inhibitors is not recommended.

| Concomitant Drug Class: Drug Name | Effect on Concentration† | Clinical Comment |
|--------------------------------------|--------------------------|---|
| Antibiotics: nafcillin | ↓ EBR ↓ GZR | Co-administration of grazoprevir/elbasvir with nafcillin, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of grazoprevir/elbasvir. Co-administration is not recommended. |
| Antifungals: ketoconazole‡ | ↑ EBR ↑ GZR | Concomitant use of systemic ketoconazole and grazoprevir/elbasvir increases grazoprevir exposure and may increase the overall risk of hepatotoxicity; coadministration of ketoconazole is not recommended. |
| Endothelin Antagonists: | ↓ EBR | Co-administration of grazoprevir/elbasvir with bosentan, |

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|--|--|---|
| bosentan | ↓ GZR | a moderate CYP3A inducer, may decrease elbasvir and grazoprevir concentrations, leading to reduced therapeutic effect of grazoprevir/elbasvir. Co-administration is not recommended. |
| Immunosuppressants: tacrolimus‡ | ↑ tacrolimus | Co-administration of grazoprevir/elbasvir with systemic tacrolimus increases the concentrations of tacrolimus. Frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of co-administration is recommended. |
| HIV Medications: | | |
| etravirine | ↓ EBR ↓ GZR | Co-administration of grazoprevir/elbasvir with etravirine, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of grazoprevir/elbasvir. Co-administration is not recommended. |
| elvitegravir/ cobicistat/emtricitabine/ tenofovir (disoproxil fumarate or alafenamide) | ↑ EBR ↑ GZR | Co-administration of grazoprevir/elbasvir with these cobicistat containing regimens may increase the concentrations of EBR and GZR. Co-administration is not recommended. |
| HMG-CoA Reductase Inhibitors: | | |
| atorvastatin‡ | ↑ atorvastatin | Co-administration of EBR and GZR with atorvastatin increases the concentrations of atorvastatin. The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with grazoprevir/elbasvir. |
| rosuvastatin‡ | ↑ rosuvastatin | Co-administration of EBR and GZR with rosuvastatin increases the concentrations of rosuvastatin. The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with grazoprevir/elbasvir. |
| fluvastatin lovastatin simvastatin | ↑ fluvastatin ↑ lovastatin ↑ simvastatin | Co-administration of grazoprevir/elbasvir with these statins has not been studied but may increase the concentrations of these statins. Statin-associated adverse events such as myopathy should be closely monitored. The lowest necessary dose should be used when co-administered with grazoprevir/elbasvir. |
| Wakefulness-Promoting Agents: modafinil | ↓ EBR ↓ GZR | Co-administration of grazoprevir/elbasvir with modafinil, a moderate CYP3A inducer, may decrease elbasvir and grazoprevir concentrations, leading to reduced therapeutic effect of grazoprevir/elbasvir. Co-administration is not recommended. |

*This table is not all inclusive.

† ↓ = decrease, ↑ = increase

‡These interactions have been studied in healthy adults.

COMMON ADVERSE EFFECTS¹

In patients receiving grazoprevir/elbasvir for 12 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% in placebo-controlled trials) were fatigue, headache, and nausea. In subjects receiving grazoprevir/elbasvir with ribavirin for 16 weeks, the most commonly reported adverse reactions of moderate or severe intensity (greater than or equal to 5%) were anemia and headache.

SPECIAL POPULATIONS¹

Pregnancy

No adequate human data are available to establish whether or not grazoprevir/elbasvir poses a risk to pregnancy outcomes.

Females and Males of Reproductive Potential

If grazoprevir/elbasvir is administered with ribavirin, the information for ribavirin with regard to pregnancy, testing, contraception, and infertility also applies to this combination regimen.

Pediatrics

Safety and efficacy of grazoprevir/elbasvir have not been established in pediatric patients less than 18 years of age.

Geriatrics

Clinical trials of grazoprevir/elbasvir with or without ribavirin included 187 patients aged 65 years and over. Higher elbasvir and grazoprevir plasma concentrations were observed in subjects aged 65 years and over. A higher rate of late ALT elevations was observed in subjects aged 65 years and over in clinical trials. However, no dosage adjustment of grazoprevir/elbasvir is recommended in geriatric patients.

Race

Higher elbasvir and grazoprevir plasma concentrations were observed in Asians compared to Caucasians. Asians experienced a higher rate of late ALT elevation in clinical trials. However, no dose adjustment of grazoprevir/elbasvir is recommended based on race/ethnicity.

Gender

Higher elbasvir and grazoprevir plasma concentrations were observed in females compared to males. Females experienced a higher rate of late ALT elevation in clinical trials. However, no dose adjustment of grazoprevir/elbasvir is recommended based on gender.

Hepatic Impairment

No dosage adjustment of grazoprevir/elbasvir is recommended in patients with mild hepatic impairment (Child-Pugh A). Grazoprevir/elbasvir is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) and severe hepatic impairment (Child-Pugh C). The safety and efficacy of grazoprevir/elbasvir have not been established in patients awaiting liver transplant or in liver transplant recipients.

Renal Impairment

No dosage adjustment of grazoprevir/elbasvir is recommended in patients with any degree of renal impairment including patients receiving hemodialysis.

DOSAGES¹

The recommended dosage is one tablet taken orally once daily with or without food.

Testing for the presence of virus with NS5A resistance-associated polymorphisms in genotype 1a patients is recommended prior to initiating grazoprevir/elbasvir. Sustained virologic response (SVR12) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93. Hepatic laboratory testing is recommended in all patients. HCV/HIV-1 co-infection patients should follow the same dosage recommendations as non-co-infection patients. For patients with renal impairment, including hemodialysis, no dosage adjustment of grazoprevir/elbasvir is recommended.

| Patient Population | Treatment | Duration |
|--|-------------------------------------|----------|
| Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms† | grazoprevir/elbasvir | 12 weeks |
| Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms† | grazoprevir/elbasvir + ribavirin | 16 weeks |
| Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced* | grazoprevir/elbasvir | 12 weeks |
| Genotype 1a or 1b: §PegIFN/RBV/PI-experienced¶ | grazoprevir/elbasvir + ribavirin | 12 weeks |
| Genotype 4: Treatment-naïve | grazoprevir/elbasvir | 12 weeks |
| Genotype 4: PegIFN/RBV-experienced* | grazoprevir/elbasvir + ribavirin | 16 weeks |

*Patients who have failed treatment with Peginterferon alfa + ribavirin.

†Polymorphisms at amino acid positions 28, 30, 31, or 93.

§The optimal grazoprevir/elbasvir -based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established.

¶Patients who have failed treatment with PegIFN + RBV + HCV NS3/4A protease inhibitor (PI): boceprevir, simeprevir, or telaprevir.

CLINICAL TRIALS¹

A literature search was performed using “grazoprevir” and “elbasvir” and “hepatitis C”.

The efficacy of grazoprevir/elbasvir was assessed in 2 placebo-controlled trials and 4 uncontrolled phase II and III clinical trials in 1,401 subjects with genotype (GT) 1, 4, or 6 chronic hepatitis C virus infection with compensated liver disease (with or without cirrhosis). Grazoprevir/elbasvir was administered once daily by mouth in these trials. For subjects who received ribavirin (RBV), the RBV dosage was weight-based and administered orally in two divided doses with food. Sustained virologic response (SVR) was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR12).

The efficacy of grazoprevir/elbasvir in treatment-naïve patients with genotype 1 chronic HCV with or without cirrhosis was demonstrated in the C-EDGE TN and C-EDGE COINFECTION trials. C-EDGE TN was a randomized, double-blind, placebo-controlled trial in treatment-naïve patients with genotype 1 or 4 infection with or without cirrhosis. Among patients with genotype 1 infection, 55% had genotype 1a and 45% had genotype 1b. Overall, SVR12 was achieved in 95% of patients following 12 weeks of treatment, 92% in genotype 1a, 98% in genotype 1b, 94% in the non-cirrhotic patients, and 97% in the

cirrhotic patients. C-EDGE COINFECTION was an open-label, single-arm trial in treatment-naïve HCV/HIV-1 coinfecting patients with genotype 1 or 4 infection with or without cirrhosis. Subjects received grazoprevir/elbasvir for 12 weeks. Among subjects with genotype 1 infection, 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-other chronic HCV infection. Overall, SVR12 was achieved in 95% of patients following 12 weeks of treatment, 94% in genotype 1a, 96% in genotype 1b, 94% in the non-cirrhotic patients, and 100% in the cirrhotic patients.

The efficacy of grazoprevir/elbasvir in treatment-experienced patients who failed prior pegylated-interferon (PegIFN) with RBV therapy with genotype 1 chronic HCV with or without cirrhosis was demonstrated in the C-EDGE TE. C-EDGE TE was a randomized, open-label comparative trial in subjects with genotype 1 or 4 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior therapy with PegIFN + RBV therapy. Subjects were randomized in a 1:1 ratio to one of the following treatment groups: grazoprevir/elbasvir for 12 weeks or grazoprevir/elbasvir for 16 weeks. SVR12 was achieved in 94% of patients following 12 weeks of treatment and 97% following 16 weeks of treatment. Patients treated for 12 weeks achieved an SVR12 rate of 94% in patients with genotype 1a and 94% in patients with genotype 1b. Patients treated for 16 weeks achieved an SVR12 rate of 95% in patients with genotype 1a and 100% in patients with genotype 1b.

The efficacy of grazoprevir/elbasvir in treatment-experienced patients who failed prior PegIFN with RBV and a protease inhibitor therapy with genotype 1 chronic HCV with or without cirrhosis was demonstrated in the C-SALVAGE. C-SALVAGE was an open-label single-arm trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with PegIFN + RBV. Subjects received grazoprevir/elbasvir + RBV for 12 weeks. Among these subjects, 43% had cirrhosis and 46% had baseline NS3 resistance-associated substitutions. Overall, SVR12 was achieved in 96% of subjects. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were generally consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions.

The efficacy of grazoprevir/elbasvir in patients with genotype 1 HCV and severe renal impairment including those on hemodialysis was demonstrated in the C-SURFER. C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic kidney disease (CKD) Stage 4 (eGFR 15-29 mL/min/1.73 m²) or CKD Stage 5 (eGFR <15 mL/min/1.73 m²), including subjects on hemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or PegIFN ± RBV therapy. Subjects were randomized in a 1:1 ratio to one of the following treatment groups: grazoprevir/elbasvir for 12 weeks (treatment group) or placebo for 12 weeks. Overall, an SVR12 was achieved in 94% of patients, 97% in genotype 1a, 92% in genotype 2b, 93% in dialysis patients, and 100% and 93% in patients with CKD stages 4 and 5, respectively.

The efficacy of grazoprevir/elbasvir in patients with genotype 4 chronic HCV infection was demonstrated in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SCAPE. Subjects were randomized to grazoprevir/elbasvir 12 weeks or grazoprevir/elbasvir + RBV for 12 weeks. In C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION trials combined, 64% were treatment-naïve; 22% had cirrhosis; and 30% had HCV/HIV-1 co-infection. The SVR12 rate among subjects treated with grazoprevir/elbasvir for 12 weeks was 97%. In C-EDGE TE, a total of 37 genotype 4 treatment-experienced subjects received

a 12- or 16-week grazoprevir/elbasvir with or without RBV regimen. The SVR12 rate among randomized patients treated with grazoprevir/elbasvir + RBV for 16 weeks was 100%.

OTHER DRUGS USED FOR CONDITION

Other treatment options for patients with chronic HCV genotype 1 infections include ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak™) ± ribavirin, daclatasvir (Daklinza™) + sofosbuvir (Sovaldi®), sofosbuvir (Sovaldi®) + simeprevir (Olysio®), simeprevir (Olysio®) + ribavirin + peg-interferon, and sofosbuvir (Sovaldi®) + ribavirin ± interferon.

Other treatment options for patients with chronic HCV genotype 4 infections include daily ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir (Technivie™) + ribavirin, and sofosbuvir + ribavirin ± interferon.

PLACE IN THERAPY²

Grazoprevir/elbasvir is approved for use with or without ribavirin for the treatment of chronic HCV genotypes 1 or 4 infection in adults. In clinical trials, grazoprevir/elbasvir achieved >90% SVR12 rates in treatment-naïve and treatment-experienced patients with or without cirrhosis. Furthermore, grazoprevir/elbasvir achieved >90% SVR12 rates in patients with stage 4 or 5 CKD and patients who are on dialysis. It is important to note that baseline testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended in patients with genotype 1a. Genotype 1a patients with resistance-associated polymorphisms will require combination therapy with ribavirin and a longer course of treatment to avoid a decrease in efficacy. The inclusion of grazoprevir/elbasvir in the AASLD/IDSA hepatitis C treatment recommendations is forthcoming.

REFERENCES

1 Zepatier [package insert], Whitehouse Station, NJ; Merck & Co; Jan 2016.

2 HCV Guidance: Recommendations for testing, managing, and treating hepatitis C. American Association for the Study of Liver Diseases. Available at: <http://www.hcvguidelines.org/full-report>. Accessed February 15, 2016.