

Elbasvir-Grazoprevir (*Zepatier*)

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Drug Summary

Elbasvir-grazoprevir provides a safe, effective, well-tolerated, one-pill once-daily option for the treatment-naïve and treatment-experienced patients with genotype 1 or 4 infection. Patients with genotype 1a will need resistance testing prior to initiation of therapy. The presence of a substitution at amino acid positions 28, 30, 31, or 93 (seen in up to 10-15% of genotype 1a patients) requires the addition of ribavirin and extension of therapy from 12 to 16 weeks. Based on the C-SURFER data, this regimen is a particularly attractive option for patients with HCV and severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73m²) for whom sofosbuvir-based regimens may not be optimal.

Adverse Effects

Using pooled data from phase 2 and 3 trials (N=834), the most common adverse observed in patients receiving elbasvir-grazoprevir were fatigue (11%), headache (10%), and nausea (5%). Elevations in alanine aminotransferase levels (ALT) to greater than 5 times the upper limit of normal occurred in 1% of subjects, typically occurring at or after 8 weeks of therapy, with most resolving at or after the completion of therapy. To date, the rash and photosensitivity noted with earlier protease inhibitors has not been a problem in patients receiving elbasvir-grazoprevir.

Class and Mechanism

Elbasvir-grazoprevir is an oral fixed-dose combination of an NS5A replication complex inhibitor (elbasvir), and a “later”-generation HCV NS3/4A protease inhibitor (grazoprevir). Elbasvir (formerly MK-8742) is a small-molecule inhibitor of nonstructural protein 5A and possesses in vitro activity against most major HCV genotypes and some viral variants resistant to earlier NS5A inhibitors. Grazoprevir (formerly MK-5172) is a macrocyclic compound that reversibly binds to the HCV NS3/4A protease, an enzyme responsible for cleaving and processing the HCV-encoded polyprotein. It is distinct from earlier-generation protease inhibitors in its potent in vitro activity against a broader array of HCV genotypes, as well activity against some of the major resistance-associated variants (R155K and D168Y) resulting from failure with a first-generation protease inhibitors.

Manufacturer for United States

Zepatier (ZEP-ah-teer) is a fixed-dose combination of elbasvir and grazoprevir ([Figure 1](#)) and ([Figure 2](#)). It is manufactured by Merck & Co., Inc.

Indications

The fixed dose combination elbasvir-grazoprevir (50 mg/100 mg) is FDA-approved for the treatment of chronic hepatitis C genotypes 1 or 4 with the following specific requirements based on genotype, prior treatment experience, and presence of baseline polymorphisms at amino acid positions 28, 30, 31, or 93. It is recommended that patients with HCV genotype 1a infection undergo resistance testing prior to initiation of treatment with elbasvir-grazoprevir for the presence of virus with NS5A resistance-associated polymorphisms, as this will determine the duration and addition of ribavirin to the treatment regimen. For patients with HCV/HIV-1 coinfection, the dosage and duration are the same as listed below.

Elbasvir-Grazoprevir for Genotypes 1 or 4 (with or without cirrhosis)

- Genotype 1a, treatment-naïve or peginterferon/ribavirin-experienced* (without baseline NS5A polymorphisms[^]): Elbasvir-grazoprevir for 12 weeks
- Genotype 1a, treatment-naïve or peginterferon/ribavirin-experienced* (with baseline NS5A polymorphisms[^]): Elbasvir-grazoprevir plus ribavirin for 16 weeks
- Genotype 1b, treatment-naïve or peginterferon/ribavirin-experienced*: Elbasvir-grazoprevir for 12 weeks
- Genotype 1a[#] or 1b, peginterferon/ribavirin/protease inhibitor-experienced⁺: Elbasvir-grazoprevir plus ribavirin for 12 weeks
- Genotype 4, treatment-naïve: Elbasvir-grazoprevir for 12 weeks
- Genotype 4, peginterferon/ribavirin-experienced*: Elbasvir-grazoprevir plus ribavirin for 16 weeks

*Patients who have failed therapy with peginterferon alfa plus ribavirin

[^]One or more polymorphisms at the amino acid positions 28, 30, 31, or 93.

[#]The optimal treatment duration for peginterferon/ribavirin/protease inhibitor-experienced patients with genotype 1a and one or more baseline NS5A resistance-associated polymorphisms has not been established.

⁺Patients who have failed therapy with peginterferon alfa plus ribavirin plus an HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir)

Contraindications

Elbasvir-grazoprevir is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). In addition, elbasvir-grazoprevir is contraindicated with concomitant use of organic ion transporter polypeptide 1B (OATP1B) inhibitors, strong inducers of cytochrome P450 3A (CYP3A), and efavirenz ([Figure 2](#)). When elbasvir-grazoprevir is coadministered with ribavirin, the contraindications for ribavirin apply to the use of the combination regimen.

Dosing

Elbasvir-grazoprevir is available as a fixed-dose, coformulated tablet that contains 50 mg of elbasvir and 100 mg of grazoprevir ([Figure 3](#)).

- The recommended dose is one tablet taken orally once daily, with or without food.
 - No dosage adjustment is recommended for elbasvir-grazoprevir in patients with renal insufficiency, including patients with end-stage renal disease or patients on hemodialysis.
 - For patients with mild hepatic impairment (Child-Pugh Class A), no dose adjustment of elbasvir-grazoprevir is recommended. Elbasvir-grazoprevir is contraindicated for use in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C).
 - When ribavirin is used with elbasvir-grazoprevir in patients with a CrCl greater than 50 mL/min, it should be given as weight-based dosing in two divided doses with food (weight less than 66 kg=800 mg/day; 66 to 80 kg=1000 mg/day; 81 to 105 kg=1200 mg/day; greater than 105 kg=1400 mg/day). For patients with CrCl less than 50 mL/min, the dose of ribavirin should be adjusted to be consistent with the recommendations in the ribavirin package insert.
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Clinical Use

Elbasvir-grazoprevir has primarily been studied as an all-oral (interferon-free) combination regimen in treatment-naïve and treatment-experienced patients with genotype 1 or 4 chronic HCV infection. The phase 3 C-EDGE trials have evaluated elbasvir-grazoprevir, with or without ribavirin (typically given for 12 weeks) and have demonstrated SVR12 rates in the 92 to 97% range. This combination elbasvir-grazoprevir appears to have comparable efficacy in patients with HCV and HIV coinfection as those with HCV mono-infection. The C-SURFER study demonstrated excellent SVR12 rates in patients with Stage 4 or 5 kidney disease, including those on hemodialysis. Elbasvir-grazoprevir has similar efficacy in patients with or without cirrhosis, but it should not be used in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C).

Cost and Medication Access

- Merck has an active Patient Assistance Program for patients who cannot obtain or afford elbasvir-grazoprevir. Information on the program can be obtained at Merck Patient Assistance Program ([Merck Helps](#)) website or by calling **1-800-405-5810**.
- Merck has also developed a copay assistance program. There are specific conditions that apply.

Information to help patients get access and support to elbasvir-grazoprevir is available on the [Merck Access and Support Services](#) website.

Resistance

Patients with HCV genotype 1a infection should undergo HCV RNA NS5A resistance testing prior to initiation of treatment with elbasvir-grazoprevir, since results of the resistance testing will determine treatment duration and the addition of ribavirin. This recommendation is based on data that patients with HCV genotype 1a with one or more of the HCV NS5A baseline polymorphisms at positions M28, Q30, L31, or Y93 have reduced efficacy with a 12-week treatment course of elbasvir-grazoprevir. Specifically, with the presence of one or more of these four polymorphisms in patients with genotype 1a, the SVR12 rates were 70% (39/56) with a 12-week course of elbasvir-grazoprevir. In contrast, in patients with genotype 1a (and one or more of the the four polymorphisms) the SVR rates were 100% (6/6) with a 16-week course of elbasvir-grazoprevir plus ribavirin. Accordingly, based on available data, in the presence of one or more of these polymorphisms in a patient with genotype 1a warrants the addition of ribavirin to elbasvir-grazoprevir, and extending therapy from 12 to 16 weeks. Among patients in the United States with genotype 1a enrolled in the clinical trials, the prevalence of one or more of these polymorphisms (at positions 28, 30, 31, or 93) was 12%.

Pooled analysis of drug resistance among the 50 patients who experienced treatment failure in the registration studies for elbasvir-grazoprevir revealed that treatment-emergent NS3 substitutions occurred in 78% of genotype 1a patients, 25% of genotype 1b patients, and 40% of genotype 4, with A156T and D168A occurring as the most frequent mutations in patients with genotype 1a. These two resistance-associated variants can confer resistance to grazoprevir and other protease inhibitors. Specific NS5A substitutions occurred in 81% of patients with genotype 1a who failed therapy, 88% of genotype 1b, and in all of those with genotype 4. Elbasvir remains active in vitro against M28V and Q30L genotype 1a NS5A variants and L28M/V, R30Q, L31V, and Y93C, which can confer resistance to other NS5A inhibitors. Other NS5A substitutions aside from those mentioned can reduce the activity of elbasvir against genotype 1a or 1b.

Several commercial laboratories offer HCV RNA NS5A resistance testing, including [Quest](#) and [Monogram \(Labcorp\)](#) and [Mayo Medical Laboratories](#).

Key Drug Interactions

For complete information on elbasvir-grazoprevir-related drug interactions, see the [Drug Interactions section in the Elbasvir-Grazoprevir \(Zepatier\) Prescribing Information](#).

Full Prescribing Information

Elbasvir-grazoprevir (*Zepatier*) [Full Prescribing Information](#).

Figures

[Figure 1. Pill - Elbasvir-Grazoprevir \(Zepatier\)](#)

Photograph courtesy of Merck & Co., Inc.

[Figure 2. Packaging - Elbasvir-Grazoprevir \(Zepatier\)](#)

Photograph courtesy of Merck & Co., Inc.

[Figure 3. Medication Contraindications](#)

Source: Elbasvir-Grazoprevir (Zepatier) Prescribing Information