var drug_url = "elbasvir-grazoprevir";

Elbasvir-Grazoprevir *(Zepatier)*

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Drug Summary

Elbasvir-grazoprevir provides a safe, very effective, well-tolerated, all oral, 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 and presence of a polymorphism at amino acid positions 28, 30, 31, or 93 requires addition of ribavirin and extension of therapy from 12 to 16 weeks. Based on the C-SURFER data, this regimen is particularly attractive for HCV-infected patients with advanced kidney disease. Although data are limited, the triple combination of elbasvir-grazoprevir plus sofosbuvir may provide an additional potent ribavirin-free 12-week regimen for genotype 3 patients, but more data are needed to establish whether this 12-week triple regimen is effective in cirrhotic patients with genotype 3 infection. The announced list price for elbasvir-grazoprevir ($54,600) is significantly lower than other first-line regimens and should enable broad patient access from private insurance companies and federally-funded programs.

Class and Mechanism

Elbasvir-grazoprevir (*Zepatier*) (Figure 1) 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

The fixed-dose combination medication elbasvir and grazoprevir (*Zepatier*) is manufactured by Merck & Co., Inc.

Cost and Medication Access

Merck has established a list price of $54,600 for a 12-week treatment course. For patients needing a 16-week course, the list price is $72,800.

- 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 co-pay 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.

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.

Key Drug Interactions

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

Clinical Trials

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C-EDGE CO-STAR

In this randomized, phase 3, placebo-controlled trial, investigators enrolled 301 treatment-naive patients with chronic HCV genotype 1, 4, or 6 to receive a 12-week course of elbasvir plus grazoprevir; all subjects enrolled had a history of injection drugs and all were receiving opiate agonist therapy. In the trial, 201 subjects received elbasvir plus grazoprevir at enrollment (immediate treatment arm) and 100 subjects received placebo for 12 weeks, followed by treatment with elbasvir plus grazoprevir (deferred treatment arm). At baseline, 58% of the patients in the study had a positive urine drug screen (for a substance other than an opioid agonist). Most of the patients (76%) had genotype 1 infection and 21% had cirrhosis. The SVR12 results were available only for the immediate treatment group and 95% of patients achieved an SVR12 (when excluding patients who discontinued the trial for non-treatment related reasons). The results were similar regardless of whether the baseline urine drug screen was positive. Adherence with medications was excellent, with 99% of patients taking at least 90% of the medication.

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C-EDGE Coinfection

In this prospective single-arm, open-label clinical trial, 218 patients with chronic hepatitis C genotype

1, 4, or 6 and HIV coinfection received the fixed-dose combination of elbasvir-grazoprevir once daily for 12 weeks. Nearly all (97%) patients were on antiretroviral therapy with HIV viral suppression and the median CD4 cell count was 568 cells/mm^3; 86% had genotype 1a or 1b infection and 35 (16%) had compensated cirrhosis. The overall SVR12 rate was 96% by primary analysis, with the breakdown by genotype showing 96.5% for genotype 1a, 95.5% for genotype 1b and 96.4% for genotype 4. All cirrhotic patients achieved an SVR12. When patients who did not achieve an SVR12 due to treatment discontinuation or reinfection were excluded, the overall SVR12 rate was 97%.

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C-EDGE Treatment-Experienced

In this randomized, open-label, phase 3 trial, 420 patients with genotype 1, 4, or 6 hepatitis C infection and a history of treatment failure with peginterferon and ribavirin received elbasvir-grazoprevir (50/100 mg), with or without ribavirin, for 12 or 16 weeks. Among patients who received a 12-week regimen, the SVR12 rate was 94% for elbasvir-grazoprevir with ribavirin and 92% for elbasvir-grazoprevir without ribavirin. In the 16-week treatment arms, the SVR12 rate was 97% and 92% for elbasvir-grazoprevir, with and without ribavirin respectively. Notably, of the 12 patients with genotype 1a who experienced viral relapse, 10 had evidence of a baseline NS5A resistance-associated variant.

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C-EDGE Treatment-Naive

In this randomized phase 3 trial, the safety and efficacy of the fixed-dose combination of elbasvir-grazoprevir (50/100 mg) once daily was evaluated in treatment-naïve patients with genotype 1, 4, or 6 hepatitis C infection, with or without compensated cirrhosis. Investigators randomized (in a 3:1 ratio) 421 patients to immediate versus delayed treatment arms. In the latter group, patients received a placebo for 12 weeks, followed by a 4-week interval, followed by elbasvir-grazoprevir for 12 weeks. The overall SVR12 rate was 95%, with rates of 92% for genotype 1a, 99% for genotype 1b, 100% for genotype 4, and 80% for genotype 6. Among the 70 cirrhotic patients enrolled in the trial, 97% achieved an SVR12 with no statistically significant difference compared with non-cirrhotic patients.

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C-SALVAGE

In this open-label, single-arm, phase 2 trial, treatment-experienced patients with genotype 1 HCV and previous failure of peginterferon/ribavirin (PR) and an earlier-generation protease inhibitor (boceprevir, telaprevir, or simeprevir) were treated with elbasvir plus grazoprevir and ribavirin for 12 weeks. Patients with compensated cirrhosis were permitted and comprised 43% of the total 79 patients enrolled in the study. At 24 weeks post treatment, SVR occurred in 76 (96%) patients. There were 3 relapses (2 in genotype 1a and 1 in genotype 1b); all 3 relapsers had experienced virologic failure on a prior PI-based regimen and had NS3 variants detected at baseline.

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C-SCAPE

In this phase 2, open-label, randomized trial, investigators examined the safety and efficacy of different combinations of elbasvir plus grazoprevir, with or without ribavirin, for 12 weeks in patients with HCV genotype 2 and genotypes 4, 5, or 6 infection (with and without cirrhosis). Patients with genotype 2 infection were randomized to receive (a) elbasvir 50 mg plus grazoprevir 100 mg plus ribavirin or (b) grazoprevir 100 mg on its own with ribavirin. Patients with HCV genotype 4, 5, or 6 were randomized to receive elbasvir 50 mg plus grazoprevir 100 mg, with or without ribavirin. Among patients with genotype 2 infection, 80% achieved an SVR12 with the three drug-regimen of elbasvir plus grazoprevir plus ribavirin, whereas 73% did so with dual regimen of grazoprevir plus ribavirin. In subset analysis, patients with baseline HCV RNA less than or equal to 2 million IU/mL were more likely respond than those with viral levels greater than 2 million IU/mL. The SVR12 rates were 100%, 100%, and 90% for the 18 patients with genotype 4, 5, or 6 who received elbasvir plus grazoprevir plus ribavirin (72% for the 18 patients who did not receive ribavirin).

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C-SURFER

In this phase 3, randomized study, investigators enrolled 224 patient with hepatitis C genotype 1 and chronic renal disease, including patients on hemodialysis, to receive immediate treatment with 12 weeks of therapy with elbasvir plus grazoprevir, or deferred therapy. Subjects in the deferred group received placebo during the first 12 weeks and use of placebo was considered important as a comparator for safety purposes, particularly due to safety concerns in this patient population with advanced renal disease. Overall, 80% of the patients enrolled in the trial were treatment-naive and 76% were on hemodialysis. Among the 116 patients who completed therapy, 115 (99%) achieved an SVR12. Six patients were excluded from the modified full analysis set population, but all six had HCV RNA levels less than 15 IU/ml at that time of study discontinuation. The safety profile observed in patients who received grazoprevir plus elbasvir was comparable to that seen in patients receiving placebo.

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C-SWIFT

In this open-label phase 2 trial, investigators evaluated the efficacy of shorter durations (4, 6, or 8 weeks) of fixed-dose elbasvir-grazoprevir, given in combination with sofosbuvir, in treatment-naïve patients with HCV genotype 1 (n=102) or genotype 3 (n=41) infection, with and without compensated cirrhosis. Among the genotype 1 patients without cirrhosis who were treated with 6 weeks of therapy, 87% achieved an SVR12, compared with only 33% among those who had 4 weeks of therapy. Better SVR12 rates were obtained in cirrhotic patients with genotype 1 who had 8 weeks of treatment (94%) than with 6 weeks of therapy (80%). Non-cirrhotic patients with genotype 3 infection had excellent SVR12 rates (93% with 8 weeks of therapy and 100% with 12 weeks of therapy); for the cirrhotic patients, 91% achieved an SVR12 with 12 weeks of therapy.

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C-WORTHY

In this open-label, phase 2 trial involving patients with genotype 1 hepatitis C, treatment-naïve patients with compensated cirrhosis (cohort 1, n=123) and treatment-experienced patients with a prior null response to peginterferon plus ribavirin (cohort 2, n=130) were randomized to receive elbasvir plus grazoprevir, with or without ribavirin, for 12 or 18 weeks. In the cirrhotic cohort, 90% to 97% of patients achieved an SVR12; in the null responder cohort, SVR12 occurred in 91% to 100% of patients. The SVR12 rate for null cirrhotics (historically the most treatment refractory) was 94% for genotype 1a and 100% for genotype 1b. A subgroup analysis did not show a significant benefit of adding ribavirin to elbasvir plus grazoprevir.

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C-WORTHY Coinfection

This was a randomized, open-label, phase 2 trial of elbasvir plus grazoprevir, with or without ribavirin, in treatment-naïve HCV monoinfected patients without cirrhosis or patients with HIV and HCV coinfection without cirrhosis; the C-WORTHY Coinfection was a substudy conducted within a larger C-WORTHY study. In the monoinfected group 159 patients received different combinations of elbasvir plus grazoprevir that varied by elbasvir dose (20 or 50 mg), duration (8 or 12 weeks), and addition of ribavirin. In the HCV-HIV coinfection group, 59 patients were randomized to receive either elbasvir (50 mg) plus grazoprevir (100 mg), with or without ribavirin, for 12 weeks. In the HCV-monoinfected patient group, SVR12 was achieved in 80% of patients who received 8 weeks of therapy (with ribavirin), 93% with 12 weeks of therapy (with ribavirin), and 98% with 12 weeks of therapy (without ribavirin). For the HCV coinfected patients, the SVR12 rates with 12 weeks of therapy were 97% (with ribavirin) and 87% (without ribavirin). These combinations were generally well-tolerated with fatigue, headache, and nausea the most common side effects.

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Figures

Figure 1 Packaging - Elbasvir-Grazoprevir (*Zepatier*)

Photograph courtesy of Merck & Co., Inc.

Figure 2 Medication Contraindications

Source: Elbasvir-Grazoprevir (*Zepatier*) Prescribing Information

Drugs that are Contraindicated for Use with Elbasvir-Grazoprevir*	
Organic ion transporter polypeptide 1B (OATP1B) inhibitors	
Antimycobacterials	Rifampin
HIV medications	Atazanavir Darunavir Lopinavir Saquinavir Tipranavir
Immunosuppressants	Cyclosporine
Strong CYP3A Inducers	
Anticonvulsants	Phenytoin Carbamazepine
Herbal products	St. John's Wort (Hypericum perforatum)
HIV medications	Efavirenz+

*This is not a complete list of all drugs that inhibit OAT1B or strongly induce CYP3A
+Efavirenz is listed as a strong CYP3A inducer because it reduced grazoprevir exposure by ≥80%

Figure 3 Pill - Elbasvir-Grazoprevir (*Zepatier*)

Photograph courtesy of Merck & Co., Inc.