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. The wholesale acquisition cost for elbasvir-grazoprevir ($54,600) is notably lower than other first-line regimens.

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
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

Concomitant use of elbasvir-grazoprevir with OATP1B inhibitors can cause significant increases in the plasma levels of grazoprevir; thus, these combinations are contraindicated. The concomitant use of elbasvir-grazoprevir with strong CYP3A inducers or efavirenz can result in significant lowering of elbasvir and grazoprevir plasma levels, which may result in reduced efficacy of elbasvir-grazoprevir; accordingly, these combinations are contraindicated. Use of elbasvir-grazoprevir is not recommended with moderate CYP3A inducers or with certain strong CYP3A inhibitors. For complete information on elbasvir-grazoprevir-related drug interactions, see the Drug Interactions section in the Elbasvir-Grazoprevir (Zepatier) Prescribing Information.
Figures

Figure 1 Packaging - Elbasvir-Grazoprevir (Zepatier)

Photograph courtesy of Merck & Co., Inc.
**Figure 2 Medication Contraindications**

Source: Elbasvir-Grazoprevir (Zepatier) Prescribing Information

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Example Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic ion transporter polypeptide 1B (OATP1B) inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>Rifampin</td>
</tr>
<tr>
<td>HIV medications</td>
<td>Atazanavir, Darunavir, Lopinavir, Saquinavir, Tipranavir</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td><strong>Strong CYP3A Inducers</strong></td>
<td>Phenytoin, Carbamazepine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>St. John’s Wort (Hypericum perforatum)</td>
</tr>
<tr>
<td>Herbal products</td>
<td>Efavirenz*</td>
</tr>
</tbody>
</table>

*This is not a complete list of all drugs that inhibit OATP1B 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.

Tablet may not be shown at actual size. For illustration purposes only.