

# Elbasvir and Grazoprevir

## (Systemic)

Antiviral; fixed combination containing elbasvir (HCV NS5A replication complex inhibitor [NS5A inhibitor]) and grazoprevir (HCV NS3/4A protease inhibitor).

**Class:** 8.18.40.24 • HCV Replication Complex Inhibitors (AHFS primary)

**Brands:** Zepatier®

## Uses

### Chronic HCV Infection

- Treatment of chronic HCV genotype 1 or genotype 4 infection in treatment-naïve (previously untreated) or previously treated adults, including those with compensated liver disease (with or without cirrhosis) and those with HIV coinfection.
- Used alone or in conjunction with ribavirin, depending on HCV genotype and certain patient factors (e.g., previous treatment experience, presence of baseline polymorphisms).
- Efficacy of 12-week elbasvir/grazoprevir regimen for treatment of HCV genotype 1a infection reduced when 1 or more NS5A resistance-associated polymorphisms at certain amino acid positions (28, 30, 31, 93) are present at baseline. Screening for NS5A resistance-associated polymorphisms recommended prior to initiation of treatment in patients with HCV genotype 1a infection. (See General under Dosage and Administration.)
- Treatment of chronic HCV infection is complex and rapidly evolving; consult a specialist to obtain the most up-to-date information. Information from the American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA), and International Antiviral Society–USA (IAS–USA) regarding diagnosis and management of HCV infection, including recommendations for initial treatment, is available at <http://www.hcvguidelines.org>.

## Dosage and Administration

### General

- For treatment of chronic HCV infection, elbasvir/grazoprevir is used alone or in conjunction with ribavirin.
- Base specific regimen and duration of treatment on HCV genotype and certain patient factors (e.g., previous treatment experience, presence of baseline polymorphisms). Relapse rates after treatment are affected by baseline patient and viral factors and differ between treatment regimens and treatment duration for certain subgroups.
- HCV genotype 1a infection: Screening for presence of HCV NS5A resistance-associated polymorphisms recommended prior to initiation of treatment to determine appropriate treatment regimen and treatment duration.
- Prior to and during treatment, perform appropriate laboratory tests to evaluate liver function. (See Hepatic Effects under Cautions.)

### Administration

#### Oral Administration

Administer orally once daily without regard to food.

### Dosage

Available as fixed-combination tablets containing 50 mg of elbasvir and 100 mg of grazoprevir.

### Adults

#### Treatment of Chronic HCV Infection

##### >HCV Genotype 1a Infection

**Oral:** 1 tablet (elbasvir 50 mg and grazoprevir 100 mg) once daily.

Use alone in patients *without* baseline NS5A polymorphisms who are treatment-naïve or previously treated with peginterferon alfa and ribavirin; use in conjunction *with* ribavirin in those *with* baseline NS5A polymorphisms or in those previously treated with peginterferon alfa, ribavirin, and an HCV protease inhibitor. Treatment duration of 12 weeks recommended in most patients; treatment duration of 16 weeks recommended in those *with* baseline NS5A polymorphisms. (See Table 1.)

**Table 1. Recommended Treatment Regimen and Duration of Elbasvir/ Grazoprevir for HCV Genotype 1a Infection in Adults with or without Cirrhosis.**

Patient Type	Multiple-drug Regimen	Duration of Treatment
Treatment-naïve or previously treated <sup>a</sup> <i>without</i> baseline NS5A polymorphisms <sup>b</sup>	Elbasvir/grazoprevir	12 weeks
Treatment-naïve or previously treated <sup>a</sup> <i>with</i> baseline NS5A polymorphisms <sup>b</sup>	Elbasvir/grazoprevir <i>with</i> ribavirin <sup>c</sup>	16 weeks
Previously treated with an HCV protease inhibitor <sup>d,e</sup>	Elbasvir/grazoprevir <i>with</i> ribavirin <sup>c</sup>	12 weeks

<sup>a</sup>Previously treated defined as patients who failed treatment with peginterferon alfa and ribavirin.

<sup>b</sup>NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93.

<sup>c</sup>Use weight-based ribavirin dosage in patients with  $Cl_{cr} > 50$  mL/minute (800 mg daily in those  $< 66$  kg, 1 g daily in those 66–80 kg, 1.2 g daily in those 81–105 kg, 1.4 g daily in those  $> 105$  kg); give ribavirin daily dosage in 2 divided doses with food.

<sup>d</sup>Previously treated with an HCV protease inhibitor defined as patients who failed treatment with a regimen of peginterferon alfa, ribavirin, and an HCV NS3/4A protease inhibitor (e.g., boceprevir, simeprevir, telaprevir).

<sup>e</sup>The optimal elbasvir/grazoprevir-based regimen and duration of treatment not established for patients with HCV genotype 1a infection who were previously treated with peginterferon alfa, ribavirin, and an HCV protease inhibitor and have 1 or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93.

### >HCV Genotype 1b Infection

**Oral:** 1 tablet (elbasvir 50 mg and grazoprevir 100 mg) once daily.

Use alone in patients who are treatment-naïve or previously treated with peginterferon alfa and ribavirin; use in conjunction *with* ribavirin in those previously treated with peginterferon alfa, ribavirin, and an HCV protease inhibitor. Treatment duration of 12 weeks recommended. (See Table 2.)

**Table 2. Recommended Treatment Regimen and Duration of Elbasvir/ Grazoprevir for HCV Genotype 1b Infection in Adults with or without Cirrhosis.**

Patient Type	Multiple-drug Regimen	Duration of Treatment
Treatment-naïve or previously treated <sup>a</sup>	Elbasvir/grazoprevir	12 weeks
Previously treated with an HCV protease inhibitor <sup>b</sup>	Elbasvir/grazoprevir <i>with</i> ribavirin <sup>c</sup>	12 weeks

<sup>a</sup>Previously treated defined as patients who failed treatment with peginterferon alfa and ribavirin.

<sup>b</sup>Previously treated with an HCV protease inhibitor defined as patients who failed treatment with a regimen of peginterferon alfa, ribavirin, and an HCV NS3/4A protease inhibitor (e.g., boceprevir, simeprevir, telaprevir).

<sup>c</sup>Use weight-based ribavirin dosage in patients with  $Cl_{cr} > 50$  mL/minute (800 mg daily in those  $< 66$  kg, 1 g daily in those 66–80 kg, 1.2 g daily in those 81–105 kg, 1.4 g daily in those  $> 105$  kg); give ribavirin daily dosage in 2 divided doses with food.

### >HCV Genotype 4 Infection

**Oral:** 1 tablet (elbasvir 50 mg and grazoprevir 100 mg) once daily.

Use alone in patients who are treatment-naïve; use in conjunction *with* ribavirin in those previously treated with peginterferon alfa and ribavirin. Treatment duration of 12 weeks recommended in treatment-naïve patients; treatment duration of 16 weeks recommended in those previously treated with peginterferon alfa and ribavirin. (See Table 3.)

**Table 3. Recommended Treatment Regimen and Duration of Elbasvir/Grazoprevir for HCV Genotype 4 Infection in Adults with or without Cirrhosis.**

Patient Type	Multiple-drug Regimen	Duration of Treatment
Treatment-naïve	Elbasvir/grazoprevir	12 weeks
Previously treated <sup>a</sup>	Elbasvir/grazoprevir <i>with</i> ribavirin <sup>b</sup>	16 weeks

<sup>a</sup>Previously treated defined as patients who failed treatment with peginterferon alfa and ribavirin.

<sup>b</sup>Use weight-based ribavirin dosage in patients with  $Cl_{cr} > 50$  mL/minute (800 mg daily in those <66 kg, 1 g daily in those 66–80 kg, 1.2 g daily in those 81–105 kg, 1.4 g daily in those >105 kg); give ribavirin daily dosage in 2 divided doses with food.

**>HCV-infected with HIV Coinfection.**

**Oral:** HCV genotype 1 or 4: Use same elbasvir/grazoprevir dosage and same HCV genotype-specific multiple-drug regimen and duration of treatment recommended for HCV-infected patients without HIV coinfection. (See Table 1, Table 2, and Table 3.)

**Special Populations**

**Hepatic Impairment**

Mild hepatic impairment (Child-Pugh class A): Dosage adjustments not needed.  
Moderate or severe hepatic impairment (Child-Pugh class B or C): Contraindicated. (See Hepatic Impairment under Cautions.)

**Renal Impairment**

Mild, moderate, or severe renal impairment, including those requiring hemodialysis: Dosage adjustments not needed. (See Renal Impairment under Cautions.)

**Geriatric Patients**

Dosage adjustments not needed. (See Geriatric Use under Cautions.)

**Cautions**

**Contraindications**

- Moderate or severe hepatic impairment (Child-Pugh class B or C). (See Hepatic Impairment under Cautions.)
- Concomitant use with certain drugs (e.g., inhibitors of organic anion transporting polypeptide [OATP] 1B1 and 1B3, potent inducers of CYP3A, efavirenz). (See Interactions.)
- If elbasvir/grazoprevir used in conjunction *with* ribavirin, the contraindications to ribavirin also apply. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions.)

**Warnings/Precautions**

**Hepatic Effects**

Increased ALT concentrations (>5 times ULN) reported in 1% of patients in clinical trials. Generally occurs at ≥8 weeks after initiation of treatment (mean onset 10 weeks; range 6–12 weeks); typically asymptomatic and resolved with ongoing treatment or completion of treatment. Increased rates of late-onset ALT elevations reported in patients with increased grazoprevir plasma concentrations and in certain patient groups (e.g., ≥65 years of age, Asian descent, females). Incidence of late-onset ALT elevations apparently not affected by presence of cirrhosis or treatment duration.

Increased bilirubin (>2.5 times ULN) reported in 6% of patients in clinical trials receiving elbasvir/grazoprevir in conjunction *with* ribavirin compared with <1% of patients receiving elbasvir/grazoprevir alone. Bilirubin increases were predominately indirect bilirubin and typically not associated with increased ALT concentrations.

Perform hepatic laboratory testing prior to treatment, at treatment week 8, at treatment week 12 (in those receiving 16 weeks of therapy), and as clinically indicated.

Consider discontinuance of elbasvir/grazoprevir if ALT concentrations remain persistently >10 times ULN. Discontinue if ALT elevations are accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR. Advise patients to immediately contact clinician if onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces is observed.

**Interactions**

Concomitant use of elbasvir/grazoprevir and certain drugs is contraindicated or not recommended. Some drug interactions may result in loss of therapeutic effect and possible development of resistance to elbasvir/grazoprevir; other interactions may lead to adverse reactions from increased exposures of concomitant drugs or elbasvir/grazoprevir.

Consider potential for drug interactions prior to and during treatment. Review concomitant drugs during treatment; monitor patient for adverse reactions associated with the concomitant drugs. (See Interactions.)

**Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens**

Consider cautions, precautions, contraindications, and drug interactions associated with both drugs in the fixed combination. Consider cautionary information applicable to specific populations (e.g., pregnant or nursing women, individuals with hepatic or renal impairment, geriatric patients) for both elbasvir and grazoprevir.

When elbasvir/grazoprevir is used in conjunction *with* ribavirin, consider that ribavirin may cause fetal toxicity and/or death. Extreme care *must* be taken to avoid pregnancy in female patients and female partners of male patients receiving a ribavirin-containing regimen. Obtain a negative pregnancy test for female patients of childbearing potential immediately prior to initiating ribavirin; perform pregnancy tests monthly during and for 6 months after ribavirin treatment is completed. Women of childbearing potential (and their male partners) and male patients (and their female partners) must use at least 2 forms of effective contraception during and for 6 months after ribavirin treatment is completed.

**Specific Populations**

**Pregnancy**

Adequate data regarding use of elbasvir/grazoprevir in pregnant women not available. In animal studies using elbasvir or grazoprevir, no evidence of fetal harm at exposures greater than those attained with recommended human dosage.

When used in conjunction *with* ribavirin, consider that ribavirin is contraindicated in pregnant women and male partners of pregnant women. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions.)

**Lactation**

Not known whether elbasvir/grazoprevir distributes into human milk, affects human milk production, or affects breast-fed infant; both elbasvir and grazoprevir are distributed into milk in rats.

Consider benefits of breast-feeding and importance of the drug to the woman; also consider potential adverse effects on the breast-fed child from the drug or underlying maternal condition.

When used in conjunction *with* ribavirin, consider potential for adverse reactions to ribavirin in nursing infants and discontinue nursing or the ribavirin-containing regimen. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions.)

**Pediatric Use**

Safety and efficacy not established in pediatric patients <18 years of age.

**Geriatric Use**

Increased rate of late-onset ALT elevations reported in adults ≥65 years of age.

Elbasvir and grazoprevir AUCs reported in individuals ≥65 years of age increased compared with AUCs reported in younger adults.

**Hepatic Impairment**

Moderate or severe hepatic impairment (Child-Pugh class B or C): Contraindicated because increased grazoprevir plasma concentrations expected and risk of ALT elevations increased. Data insufficient regarding efficacy and safety in HCV-infected patients with moderate hepatic function.

Efficacy and safety not established in liver transplant recipients or pretransplant patients.

Mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C) without HCV infection: Elbasvir AUCs similar but grazoprevir AUCs increased (12-fold higher in those with severe hepatic impairment) compared with AUCs in individuals with normal hepatic function.

Compensated cirrhosis in HCV-infected adults: Elbasvir AUCs similar but grazoprevir AUCs slightly higher compared with those reported in HCV-infected adults without cirrhosis.

**Renal Impairment**

Severe renal impairment (including those requiring dialysis): Increased elbasvir and grazoprevir exposures compared with exposures in individuals without severe renal impairment. Not considered clinically important.

Elbasvir and grazoprevir not removed by hemodialysis; unlikely to be removed by peritoneal dialysis.

**Race**

Asians: Higher rate of late-onset ALT elevations reported in clinical trials. Elbasvir and grazoprevir AUCs estimated to be increased by 15 and 50%, respectively, compared with AUCs reported in Caucasians; dosage adjustments not needed based on race.

Black or African American individuals: Estimated elbasvir and grazoprevir exposures are comparable to those in Caucasians.

**Gender**

Females: Higher rate of late-onset ALT elevations reported in clinical trials. Elbasvir and grazoprevir AUCs estimated to be increased by 50 and 30%, respectively, compared with AUCs reported in males; dosage adjustments not needed based on gender.

### Common Adverse Effects

Elbasvir/grazoprevir: Headache, fatigue, insomnia, dizziness, nausea, diarrhea, upper respiratory tract infection, arthralgia.

Elbasvir/grazoprevir in conjunction with ribavirin: Fatigue, headache, asthenia, nausea, vomiting, diarrhea, constipation, upper abdominal pain, insomnia, anemia, decreased hemoglobin concentrations, elevated bilirubin concentrations, elevated triacylglycerol lipase concentrations.

## Interactions

Elbasvir and grazoprevir are substrates of CYP3A; grazoprevir is a weak inhibitor of CYP3A. Elbasvir and grazoprevir inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6.

Elbasvir inhibits P-gp transport system; elbasvir and grazoprevir are substrates of P-gp.

Elbasvir and grazoprevir inhibit intestinal breast cancer resistance protein (BCRP).

Grazoprevir is a substrate and inhibitor of OATP1B1 and 1B3.

The following drug interactions based on studies using elbasvir/grazoprevir, elbasvir alone, or grazoprevir alone, or are predicted drug interactions that may occur with elbasvir/grazoprevir. When elbasvir/grazoprevir is used, consider interactions associated with both drugs in the fixed combination.

### Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes

Potent CYP3A inducers: Possible pharmacokinetic interactions (decreased elbasvir and grazoprevir concentrations and possible loss of therapeutic effect); concomitant use contraindicated.

Moderate CYP3A inducers: Possible pharmacokinetic interactions (decreased elbasvir and grazoprevir concentrations and possible reduced therapeutic effect); concomitant use not recommended.

Potent CYP3A inhibitors: Possible pharmacokinetic interactions (increased elbasvir and grazoprevir concentrations); concomitant use not recommended.

### Drugs Affecting or Affected by Breast Cancer Resistance Protein

BCRP substrates: Possible pharmacokinetic interactions (increased concentrations of BCRP substrate).

### Drugs Affecting or Affected by Organic Anion Transport Polypeptides

OATP1B1 or 1B3 inhibitors: Possible pharmacokinetic interactions (increased grazoprevir concentrations); concomitant use contraindicated.

### Specific Drugs

Drug	Interaction	Comments
<b>Abacavir</b>	Clinically important pharmacokinetic interactions not expected	
<b>Antacids</b>		Dosage adjustments not needed if used concomitantly with antacids
<b>Anticonvulsants (carbamazepine, phenytoin)</b>	Carbamazepine, phenytoin: Possible decreased elbasvir and grazoprevir concentrations; possible loss of virologic response to the HCV antiviral	Carbamazepine, phenytoin: Concomitant use contraindicated
<b>Antifungals, azoles (ketoconazole)</b>	Ketoconazole: Increased elbasvir and grazoprevir concentrations and AUC; may increase risk of hepatotoxicity	Concomitant use not recommended
<b>Antimycobacterials, rifamycins (rifampin)</b>	Rifampin: Multiple doses result in clinically important decreases in grazoprevir concentrations and is expected to result in clinically important	Concomitant use contraindicated

	decreases in elbasvir concentrations; may lead to loss of virologic response to the HCV antiviral	
<b>Atazanavir</b>	<i>Ritonavir-boosted</i> atazanavir: Increased elbasvir concentrations and substantially increased grazoprevir concentrations; may increase risk of ALT elevations	<i>Ritonavir-boosted</i> atazanavir: Concomitant use contraindicated
<b>Benzodiazepines (midazolam)</b>	Midazolam: Increased midazolam exposures	
<b>Bosentan</b>	Possible decreased elbasvir and grazoprevir concentrations; possible reduced therapeutic effect of the HCV antiviral	Concomitant use not recommended
<b>Buprenorphine</b>	Fixed combination of buprenorphine and naloxone (buprenorphine/naloxone): No clinically important effects on elbasvir or grazoprevir pharmacokinetics	Dosage adjustments not needed
<b>Corticosteroids (prednisone)</b>	Prednisone: No clinically important effects on elbasvir, grazoprevir, or prednisone pharmacokinetics	Dosage adjustments not needed
<b>Darunavir</b>	<i>Ritonavir-boosted</i> darunavir: Increased elbasvir concentrations and substantially increased grazoprevir concentrations; may increase risk of ALT elevations	<i>Ritonavir-boosted</i> darunavir: Concomitant use contraindicated
<b>Digoxin</b>	No clinically important effects on digoxin pharmacokinetics	Dosage adjustments not needed
<b>Dolutegravir</b>	No clinically important effects on elbasvir, grazoprevir, or dolutegravir pharmacokinetics	Dosage adjustments not needed
<b>Efavirenz</b>	Substantially decreased elbasvir and grazoprevir concentrations; possible loss of virologic response to the HCV antiviral	Concomitant use contraindicated
<b>Elvitegravir</b>	Fixed combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (EVG/c/FTC/TDF): Possible increased elbasvir and grazoprevir concentrations  Fixed combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	EVG/c/FTC/TDF or EVG/c/FTC/TAF: Concomitant use not recommended

	(EVG/c/FTC/TAF): Possible increased elbasvir and grazoprevir concentrations	
<b>Emtricitabine</b>	Clinically important pharmacokinetic interactions not expected	
<b>Entecavir</b>	Clinically important pharmacokinetic interactions not expected	
<b>Estrogens/progestins</b>	Oral contraceptive containing ethinyl estradiol and levonorgestrel: No clinically important effects on pharmacokinetics of ethinyl estradiol or levonorgestrel	Dosage adjustments not needed
<b>Etravirine</b>	Possible decreased elbasvir and grazoprevir concentrations; possible reduced therapeutic effect of the HCV antiviral	Concomitant use not recommended
<b>Histamine H<sub>2</sub>-receptor antagonists (famotidine)</b>	Famotidine: No clinically important effects on elbasvir or grazoprevir pharmacokinetics	Histamine H <sub>2</sub> -receptor antagonists: Dosage adjustments not needed
<b>HMG-CoA reductase inhibitors (statins)</b>	Atorvastatin: Increased atorvastatin concentrations and AUC Fluvastatin, lovastatin, simvastatin: Possible increased statin concentrations Pitavastatin, pravastatin: No clinically important effects on pitavastatin or pravastatin pharmacokinetics Rosuvastatin: Increased rosuvastatin concentrations and AUC	Atorvastatin: Do not exceed atorvastatin dosage of 20 mg once daily Fluvastatin, lovastatin, simvastatin: Use lowest necessary statin dosage; monitor for statin-associated adverse effects (e.g., myopathy) Pitavastatin, pravastatin: Dosage adjustments not needed Rosuvastatin: Do not exceed rosuvastatin dosage of 10 mg once daily
<b>Immunosuppressants (cyclosporine, tacrolimus)</b>	Cyclosporine: Increased elbasvir concentrations and AUC; substantially increased grazoprevir concentrations and AUC; may increase risk of ALT elevations Tacrolimus: Increased tacrolimus concentrations; no effect on elbasvir and grazoprevir concentrations	Cyclosporine: Concomitant use contraindicated Tacrolimus: Frequently monitor tacrolimus whole blood concentrations, renal function, and tacrolimus-associated adverse effects
<b>Lamivudine</b>	Clinically important pharmacokinetic interactions not expected	
<b>Lopinavir</b>	Fixed combination of lopinavir and ritonavir (lopinavir/ritonavir): Increased	Concomitant use contraindicated

	elbasvir concentrations and substantially increased grazoprevir concentrations; may increase risk of ALT elevations	
<b>Methadone</b>	No clinically important effects on elbasvir or grazoprevir pharmacokinetics	Dosage adjustments not needed
<b>Modafinil</b>	Possible decreased elbasvir and grazoprevir concentrations; possible reduced therapeutic effect of the HCV antiviral	Concomitant use not recommended
<b>Montelukast</b>	No clinically important effects on montelukast pharmacokinetics	
<b>Mycophenolate mofetil</b>	No clinically important effects on elbasvir, grazoprevir, or mycophenolic acid pharmacokinetics	Dosage adjustments not needed
<b>Nafcillin</b>	Possible decreased elbasvir and grazoprevir concentrations; possible reduced therapeutic effect of the HCV antiviral	Concomitant use not recommended
<b>Phosphate binders (calcium acetate, sevelamer)</b>	Calcium acetate, sevelamer: No clinically important effects on elbasvir or grazoprevir pharmacokinetics	Phosphate binders: Dosage adjustments not needed
<b>Proton-pump inhibitors (pantoprazole)</b>	Pantoprazole: No clinically important effects on elbasvir or grazoprevir pharmacokinetics	Proton-pump inhibitors: Dosage adjustments not needed
<b>Raltegravir</b>	No clinically important effects on elbasvir, grazoprevir, or raltegravir pharmacokinetics	Dosage adjustments not needed
<b>Ribavirin</b>	No clinically important effects on elbasvir or grazoprevir pharmacokinetics No in vitro evidence of antagonistic anti-HCV effects	Dosage adjustments not needed
<b>Rilpivirine</b>	No clinically important effects on elbasvir, grazoprevir, or rilpivirine pharmacokinetics	Dosage adjustments not needed
<b>Ritonavir</b>	Increased grazoprevir concentrations	
<b>Saquinavir</b>	Substantially increased grazoprevir concentrations expected; may increase risk of ALT elevations	Concomitant use contraindicated
<b>Sofosbuvir</b>	No clinically important effects on sofosbuvir pharmacokinetics	Dosage adjustments not needed

<b>St. John's wort</b> ( <i>Hypericum perforatum</i> )	Substantially decreased elbasvir and grazoprevir concentrations; may lead to loss of virologic response to the HCV antiviral	Concomitant use contraindicated
<b>Tenofovir</b>	Tenofovir disoproxil fumarate (tenofovir DF): No clinically important effects on elbasvir, grazoprevir, or tenofovir pharmacokinetics	Dosage adjustments not needed
<b>Tipranavir</b>	Substantially increased grazoprevir concentrations expected; may increase risk of ALT elevations	Concomitant use contraindicated

## Pharmacokinetics

### Absorption

#### Bioavailability

Following oral administration of elbasvir/grazoprevir in HCV-infected adults, peak plasma concentrations of elbasvir and grazoprevir occur approximately 3 and 2 hours, respectively, after the dose.

Steady-state concentrations of elbasvir and grazoprevir attained within approximately 6 days with once-daily administration.

Elbasvir: Pharmacokinetics similar in healthy and HCV-infected adults; exposures increase in a dose-proportional manner over dosage range of 5–200 mg once daily.

Grazoprevir: Exposures approximately twofold higher in HCV-infected adults compared with healthy adults; studies using grazoprevir dosages of 10–800 mg once daily in HCV-infected adults indicate peak plasma concentrations and AUC increase in a more-than-dose-proportional manner.

Concomitant use of elbasvir and grazoprevir does not have a clinically important effect on pharmacokinetics of either drug compared with administration alone.

#### Food

Elbasvir and grazoprevir: Effect of food not considered clinically important.

Administration of elbasvir/grazoprevir with a high-fat meal (approximately 900 kcal, 500 kcal from fat) in healthy individuals decreases elbasvir AUC and peak plasma concentrations by approximately 11 and 15%, respectively, and increases grazoprevir AUC and peak plasma concentrations by approximately 1.5- and 2.8-fold, respectively, relative to administration in the fasting state.

#### Special Populations

Elbasvir: In individuals with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C) without HCV infection, no clinically important differences in AUCs compared with individuals with normal hepatic function.

Grazoprevir: In individuals with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C) without HCV infection, AUCs increased by 1.7-, 5-, or 12-fold, respectively, compared with individuals with normal hepatic function.

Elbasvir: In individuals with severe renal impairment (not dependent on dialysis) or individuals requiring hemodialysis, AUCs increased by 46 or 25%, respectively, compared with individuals without severe renal impairment.

Grazoprevir: In individuals with severe renal impairment (not dependent on dialysis) or individuals requiring hemodialysis, AUCs increased by 40 or 10%, respectively, compared with individuals without severe renal impairment.

Adults ≥65 years of age: Elbasvir and grazoprevir AUCs estimated to be increased by 16 and 45%, respectively, compared with AUCs in younger adults.

Asians: Elbasvir and grazoprevir AUCs estimated to be increased by 15 and 50%, respectively, compared with Caucasians.

Black or African Americans: Elbasvir and grazoprevir AUCs comparable to those in Caucasians.

Females: Elbasvir and grazoprevir AUCs estimated to be increased by 50 and 30%, respectively, compared with males.

### Distribution

#### Extent

Elbasvir: Distributes into most tissues, including the liver, based on preclinical studies.

Grazoprevir: Distributes principally into the liver, based on preclinical studies; distribution into liver probably facilitated by active transport through OATP1B1 and 1B3.

#### Plasma Protein Binding

Elbasvir: 99.9%.

Grazoprevir: 98.8%.

### Elimination

#### Metabolism

Elbasvir and grazoprevir both partially eliminated by oxidative metabolism, principally by CYP3A.

#### Elimination Route

Elbasvir and grazoprevir: >90% of dose excreted in feces; <1% excreted in urine.

#### Half-life

Elbasvir: Approximately 24 hours in HCV-infected adults.

Grazoprevir: Approximately 31 hours in HCV-infected adults.

#### Special Populations

Elbasvir and grazoprevir: Not removed by hemodialysis; removal by peritoneal dialysis unlikely since highly bound to plasma protein.

## Stability

### Storage

#### Oral

##### **Film-coated Tablets**

20–25°C (may be exposed to 15–30°C).

Protect from moisture by storing in original blister package until used.

## Actions

- Elbasvir/grazoprevir is a fixed combination of 2 HCV antivirals. Elbasvir is an HCV NS5A replication complex inhibitor (NS5A inhibitor) and grazoprevir is an HCV NS3/4A protease inhibitor.
- Elbasvir and grazoprevir are both direct-acting antivirals (DAAs) with activity against HCV. No in vitro evidence of antagonistic anti-HCV effects between the drugs in HCV replicon studies.
- Elbasvir targets HCV NS5A protein, which is required for viral replication and virion assembly. In vitro studies using cell-based replicon assays indicate elbasvir has activity against HCV genotypes 1a, 1b, and 4.
- Grazoprevir inhibits HCV NS3/4A protease, which is required for viral replication. Inhibition of NS3/4A protease prevents proteolytic cleavage of the HCV-encoded polyprotein to form mature forms of NS3, NS4A, NS4B, NS5A, and NS5B. In vitro studies using cell-based replicon assays indicate grazoprevir has activity against HCV genotypes 1a, 1b, and 4.
- Certain amino acid substitutions in NS5A of HCV genotypes 1a, 1b, and 4 selected in cell culture and associated with reduced susceptibility to elbasvir in vitro in replicon studies. Single M28A/G/T, Q30D/E/H/K/R, L31M/V, H28D, and Y93C/H/N substitutions in HCV genotype 1a replicons confer reduced susceptibility to elbasvir; single L28M, L31F, and Y93H substitutions in HCV genotype 1b replicons are associated with reduced susceptibility to elbasvir. In HCV genotype 4 replicons, single L30S, M31V, and Y93H substitutions are associated with reduced susceptibility to elbasvir. In general, combinations of elbasvir resistance-associated substitutions further reduce elbasvir antiviral activity in HCV genotypes 1a, 1b, and 4 replicons. In phase 2 and 3 clinical trials, treatment-emergent amino acid substitutions in NS5A were detected in patients with HCV genotype 1a infection (M28A/G/T, Q30H/K/R/Y, L31F/M/V, H58D, Y93H/N/S), HCV genotype 1b infection (L28M, L31F/V, Y93H), or HCV genotype 4 infection (L28S/T, M31I/V, P58D, Y93H) experiencing virologic failure.
- Certain amino acid substitutions in NS3 of HCV genotypes 1a, 1b, and 4 selected in cell culture and associated with reduced susceptibility to grazoprevir in vitro in replicon studies. Single Y56H, R155K, A156G/T/V, and D168A/E/G/N/S/V/Y substitutions in HCV genotype 1a replicons confer reduced susceptibility to grazoprevir; single F43S, Y56F, V107I, A156S/T/V, and D168A/G/V substitutions in HCV genotype 1b replicons confer reduced susceptibility to grazoprevir. In HCV genotype 4 replicons, single D168A/V substitutions are associated with reduced susceptibility to grazoprevir. In general, combinations of grazoprevir resistance-associated substitutions further reduce grazoprevir antiviral activity in HCV genotypes 1a, 1b, and 4 replicons. In phase 2 and 3 clinical trials, treatment-emergent amino acid substitutions in NS3 were detected in patients with HCV genotype 1a infection (V36L/M, Y56H, V107I, R155I/K, A156G/T/V, V158A, D168A/G/N/V/Y), HCV genotype 1b infection (Y56F, V107I, A156T), or HCV genotype 4 infection (A156M/T/V, D168A/G, V170I) experiencing virologic failure.
- Possible cross-resistance among HCV NS5A inhibitors and among HCV NS3/4A protease inhibitors. Efficacy of elbasvir/grazoprevir not established in patients who failed previous

treatment with a regimen that included an HCV NS5A inhibitor. Only limited data available regarding efficacy of elbasvir/grazoprevir in patients who failed previous treatment with a regimen of peginterferon alfa, ribavirin, and an HCV NS3/4A protease inhibitor (e.g., boceprevir, simeprevir, telaprevir) and have HCV NS3 resistance-associated substitutions at baseline prior to administration of elbasvir/grazoprevir. Elbasvir and grazoprevir active against HCV with amino acid substitutions associated with resistance to HCV NS5B polymerase inhibitors.

## Advice to Patients

- Advise patients to take elbasvir/grazoprevir once daily (with or without food) on a regular dosing schedule.
- Advise patients to store elbasvir/grazoprevir in the original container to protect the drug from moisture.
- Importance of taking the recommended dosage of elbasvir/grazoprevir for the recommended duration of treatment; importance of not missing or skipping doses.
- Advise patients to watch for early warning signs of liver inflammation (e.g., fatigue, weakness, lack of appetite, nausea and vomiting) as well as later signs (e.g., jaundice, discolored feces) and to immediately contact clinician if such manifestations occur.
- Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and dietary or herbal supplements, as well as any concomitant illnesses.
- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. If used in conjunction with ribavirin, advise men and women of importance of using 2 forms of effective contraception during and for 6 months after ribavirin therapy. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions.)
- Importance of informing patients of other important precautionary information. (See Cautions.)

## Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

### Elbasvir and Grazoprevir

#### Oral

Tablets, film-coated

Elbasvir 50 mg and  
Grazoprevir 100 mg

**Zepatier**<sup>®</sup>, Merck