Elbasvir and Grazoprevir

8:18.40.24 • HCV Replication Complex Inhibitors (AHFS primary)

■ Elbasvir and grazoprevir (elbasvir/grazoprevir) is a fixed combination containing 2 hepatitis C virus (HCV) antivirals; elbasvir is an HCV nonstructural 5A (NS5A) replication complex inhibitor (NS5A inhibitor) and grazoprevir is an HCV nonstructural 3/4A (NS3/4A) protease inhibitor.

Uses

■ Chronic Hepatitis C Virus Infection

The fixed combination of elbasvir and grazoprevir (elbasvir/grazoprevir) is used for the treatment of chronic hepatitis C virus (HCV) genotype 1 or genotype 4 infection in adults who are treatment-naive (previously untreated) or in whom prior treatment with peginterferon alfa and ribavirin (with or without an HCV protease inhibitor) failed, including those with compensated liver disease (with or without cirrhosis) and those with human immunodeficiency virus (HIV) coinfection.

Elbasvir/grazoprevir is used alone or in conjunction with ribavirin, depending on HCV genotype and certain patient factors (e.g., previous treatment experience, presence of baseline polymorphisms).

Because efficacy of a 12-week regimen of elbasvir/grazoprevir for the treatment of HCV genotype 1a infection is 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 is recommended prior to initiation of treatment in patients with HCV genotype 1a infection. (See Dosage and Administration: General.)

Because the treatment of chronic HCV infection is complex and rapidly evolving, it is recommended that treatment be directed by clinicians who are familiar with the disease and that a specialist be consulted 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.

HCV Genotype 1 Infection

Treatment-naive Adults.

Efficacy and safety of elbasvir/grazoprevir for the treatment of chronic HCV genotype 1 infection in treatment-naive adults have been evaluated in a randomized, double-blind, placebo-controlled, phase 3 trial (C-EDGE TN; NCT02105467). A total of 421 treatment-naive adults with chronic HCV genotype 1, 4, or 6 infection (noncirrhotic or with compensated cirrhosis) were randomized in a 3:1 ratio to receive elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) or placebo for 12 weeks. Those with decompensated liver disease and those with HIV coinfection were excluded. Patients who initially received placebo then received open-label elbasvir/grazoprevir for 12 weeks (deferred-treatment group). The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12; defined as plasma HCV RNA level less than 15 IU/mL [the lower limit of quantification] at 12 weeks after end of treatment). The study included 382 patients with HCV genotype 1 infection (288 in the immediate-treatment group, 94 in the deferred-treatment group); among those in the immediate-treatment group, the median age was 55 years, 56% were male, 72% had baseline HCV RNA levels exceeding 800,000 IU/mL, 55% had HCV genotype 1a infection, 67% had non-CC IL28B alleles, and 24% had cirrhosis. SVR12 was achieved in 95% of patients with HCV genotype 1 infection in the immediate-treatment group (92 or 98% of those with HCV genotype 1a or 1b infection, respectively).

Previously Treated Adults.

Efficacy and safety of elbasvir/grazoprevir for the treatment of chronic HCV genotype 1 infection in previously treated adults have been evaluated in a randomized, open-label, phase 3 trial (C-EDGE TE) and a single-arm, open-label, phase 2 trial (C-SALVAGE). The primary end point in both studies was SVR12 (defined as plasma HCV RNA level less than 15 IU/mL [the lower limit of quantification] at 12 weeks after end of treatment).

C-EDGE TE (NCT02105701) included 414 noncirrhotic or cirrhotic adults with chronic HCV genotype 1 or genotype 4 infection (with or without HIV coinfection) who previously failed a treatment regimen of peginterferon alfa and ribavirin. Patients were randomized in a 1:1:1:1 ratio to receive elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) for 12 or 16 weeks or elbasvir/grazoprevir once daily in conjunction *with* ribavirin for 12 or 16 weeks. C-EDGE TE included approximately 374 previously treated patients with HCV genotype 1 infection (median age 57 years, 64% male, 78% with baseline HCV RNA levels exceeding 800,000 IU/mL, 60% with HCV genotype 1a infection, 79% with non-CC IL28B alleles, 34% with cirrhosis). In those with HCV genotype 1 infection, SVR12 was achieved in 94% of patients treated with elbasvir/grazoprevir alone for 12 weeks and in 97% of those treated with elbasvir/grazoprevir *with* ribavirin for 16 weeks.

C-SALVAGE (NCT02105454) included 79 noncirrhotic or cirrhotic adults with HCV genotype 1 infection who previously failed a treatment regimen of peginterferon alfa, ribavirin, and an HCV protease inhibitor (e.g., boceprevir, simeprevir, telaprevir) (median age 55 years, 58% male, 63% with baseline HCV RNA levels exceeding 800,000 IU/mL, 38% with HCV genotype 1a infection, 97% with non-CC IL28B alleles, 43% with cirrhosis, 46% with baseline NS3 resistance-associated substitutions). All patients received elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) in conjunction *with* ribavirin for 12 weeks. SVR12 was achieved in 96% of patients overall; 4% of patients did not achieve SVR12 and experienced relapse after the end of treatment. The SVR12 rates were similar in those with HCV genotype 1a or 1b infection, cirrhotic or noncirrhotic patients, and those with varying response to previous HCV treatments. All patients who achieved SVR12 also achieved SVR24 (defined as plasma HCV RNA level less than 15 IU/mL [the lower limit of quantification] at 24 weeks after end of treatment).

HCV Genotype 4 Infection

Treatment-naive Adults.

Efficacy and safety of elbasvir/grazoprevir for the treatment of chronic HCV genotype 4 infection in treatment-naive adults have been evaluated in a randomized, open-label, phase 2 trial (C-SCAPE), a randomized, double-blind, placebo-controlled, phase 3 trial (C-EDGE TN), and an open-label, single-arm, phase 3 trial (C-EDGE COINFECTION).

In C-SCAPE (NCT01932762), 20 treatment-naive, noncirrhotic adults with HCV genotype 4 infection were randomized to receive elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) alone or in conjunction *with* ribavirin for 12 weeks. The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12; defined as plasma HCV RNA level less than 25 IU/mL [the lower limit of quantification] at 12 weeks after end of treatment).

In C-EDGE TN (NCT02105467), treatment-naive adults with chronic HCV genotype 1, 4, or 6 infection (without cirrhosis or with compensated cirrhosis) were randomized in a 3:1 ratio to receive elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) or placebo for 12 weeks. Those who initially received placebo then received open-label elbasvir/grazoprevir for 12 weeks (deferred-treatment group). The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12; defined as plasma HCV RNA level less than 15 IU/mL [the lower limit of quantification] at 12 weeks after end of treatment). The immediate-treatment group in C-EDGE TN included 18 treatment-naive patients with HCV genotype 4 infection.

In C-EDGE COINFECTION (NCT02105662), treatment-naive adults with HCV genotype 1, 4, or 6 infection coinfected with HIV received elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) for 12 weeks. The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12; defined as plasma HCV RNA level less than 15 IU/mL [the lower limit of quantification] at 12 weeks after end of treatment). C-EDGE COINFECTION included 28 treatment-naive patients with HCV genotype 4 infection.

When data from these 3 studies were combined, a total of 66 treatment-naive adults with HCV genotype 4 infection received 12 weeks of treatment with elbasvir/grazoprevir and SVR12 was achieved in 97% of these patients.

Previously Treated Adults.

Efficacy and safety of elbasvir/grazoprevir for the treatment of chronic HCV genotype 4 infection in previously treated adults have been evaluated in a randomized, open-label, phase 3 trial, C-EDGE TE (NCT02105701). This trial included cirrhotic or noncirrhotic adults with chronic HCV genotype 1, 4, or 6 (with or without HIV coinfection) who previously failed a treatment regimen of peginterferon alfa and ribavirin. Patients were randomized in a 1:1:1:1 ratio to receive elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) for 12 or 16 weeks or elbasvir/grazoprevir once daily in conjunction *with* ribavirin for 12 or 16 weeks. The primary end point was SVR12 (defined as plasma HCV RNA level less than 15 IU/mL [the lower limit of quantification] at 12 weeks after end of treatment). In C-EDGE TE, a total of 37 previously treated patients with HCV genotype 4 infection received a 12- or 16-week regimen of elbasvir/grazoprevir with or without ribavirin. Among the 8 patients who received a 16-week regimen of elbasvir/grazoprevir *with* ribavirin, the SVR12 rate was 100%.

HCV-infected Individuals Coinfected with HIV

Efficacy and safety of elbasvir/grazoprevir for the treatment of HCV genotype 1, 4, or 6 infection in treatment-naive adults coinfected with HIV have been evaluated in an open-label, single-arm, phase 3 study (C-EDGE COINFECTION; NCT02105662). A total of 218 HCV-infected patients who were coinfected with HIV (mean age 49 years, 84% male, 58% with baseline HCV RNA levels exceeding 800,000 IU/mL, 66% with HCV genotype 1a infection, 20% with HCV genotype 1b infection, 13% with HCV genotype 4 infection, 1% with HCV genotype 6 infection, 65% with non-CC IL28B alleles, 16% with METAVIR F4 [cirrhosis], 97% receiving HIV antiretroviral

therapy and with undetectable HIV RNA levels) received elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) for 12 weeks. The primary end point was SVR12 (defined as plasma HCV RNA level less than 15 IU/mL [the lower limit of quantification] at 12 weeks after end of treatment). SVR12 was achieved in 96% of patients overall (97, 96, or 96% of those with HCV genotype 1a, 1b, or 4 infection, respectively).

HCV-infected Individuals with Severe Renal Impairment

Efficacy and safety of elbasvir/grazoprevir for the treatment of HCV genotype 1 infection in treatment-naive or previously treated adults with severe renal impairment were evaluated in a randomized, double-blind, placebo-controlled phase 3 study (C-SURFER; NCT02092350). A total of 235 patients with compensated liver disease (with or without cirrhosis) and with stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate [eGFR] 15–29 mL/minute per 1.73 m^2 or less than 15 mL/minute per 1.73 m^2, respectively, including those undergoing hemodialysis) were randomized in a 1:1 ratio to receive elbasvir/grazoprevir (a fixed-combination tablet containing 50 mg of elbasvir and 100 mg of grazoprevir once daily) or placebo for 12 weeks. Patients who initially received placebo then received open-label elbasvir/grazoprevir for 12 weeks (deferred-treatment group). In addition, 11 patients in an intensive pharmacokinetic group received open-label treatment with elbasvir/grazoprevir once daily for 12 weeks. The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12; defined as plasma HCV RNA level less than 15 IU/mL [the lower limit of quantification] at 12 weeks after end of treatment). A total of 122 patients were included in the immediate-treatment group and intensive pharmacokinetic group (median age 58 years, 75% male, 57% with baseline HCV RNA levels exceeding 800,000 IU/mL, 72% with non-CC IL28B alleles, 52% with HCV genotype 1a infection, 6% with cirrhosis). SVR12 was achieved in 94% of patients in the pooled immediate-treatment group and intensive pharmacokinetic group (97 or 92% of those with HCV genotype 1a or 1b infection, respectively). SVR12 was achieved in 95% of those without cirrhosis compared with 86% of those with cirrhosis and in 100% of those with stage 4 renal impairment compared with 93% of those with stage 5 renal impairment.

Dosage and Administration

■ General

For the treatment of chronic hepatitis C virus (HCV) infection, elbasvir and grazoprevir (elbasvir/grazoprevir) is used alone or in conjunction with ribavirin.

The specific regimen and duration of treatment is based on HCV genotype and certain patient factors (e.g., previous treatment experience, presence of baseline polymorphisms). Relapse rates following treatment are affected by baseline patient and viral factors and differ between treatment regimens and treatment duration for certain subgroups.

Screening for the presence of HCV nonstructural 5A (NS5A) resistance-associated polymorphisms is recommended prior to initiation of elbasvir/grazoprevir in patients with HCV genotype 1a infection to determine the appropriate treatment regimen and treatment duration.

Prior to and during treatment, appropriate laboratory tests should be performed to evaluate liver function. (See Hepatic Effects under Cautions: Warnings/Precautions.)

■ Administration

Elbasvir/grazoprevir is administered orally once daily without regard to food.

■ Dosage

Elbasvir/grazoprevir is commercially available as fixed-combination tablets containing 50 mg of elbasvir and 100 mg of grazoprevir.

Chronic Hepatitis C Virus Infection

HCV Genotype 1a Infection.

For the treatment of HCV genotype 1a infection in adults, the recommended dosage of elbasvir/grazoprevir is 1 tablet (50 mg of elbasvir and 100 mg of grazoprevir) once daily. Elbasvir/grazoprevir is used alone in patients *without* baseline NS5A polymorphisms who are treatment-naive or were previously treated with peginterferon alfa and ribavirin, but is used in conjunction with ribavirin in those *with* baseline NS5A polymorphisms or in those previously treated with peginterferon alfa, ribavirin, and an HCV protease inhibitor. (See Table 1.)

A treatment duration of 12 weeks is recommended for most patients, but a treatment duration of 16 weeks is 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-naive or previously treated[a] *without* baseline NS5A polymorphisms[b]	Elbasvir/grazoprevir	12 weeks
Treatment-naive or previously treated[a] *with* baseline NS5A polymorphisms[b]	Elbasvir/grazoprevir *with* ribavirin[c]	16 weeks
Previously treated with an HCV protease inhibitor[d,e]	Elbasvir/grazoprevir *with* ribavirin[c]	12 weeks

[a]Previously treated defined as patients who failed treatment with peginterferon alfa and ribavirin.

[b]NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93.

[c]Use weight-based ribavirin dosage in patients with creatinine clearance >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.

[d]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).

[e]The optimal elbasvir/grazoprevir-based regimen and duration of treatment not established for patients with HCV genotype 1a infection who previously failed treatment 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.

For the treatment of HCV genotype 1b infection in adults, the recommended dosage of elbasvir/grazoprevir is 1 tablet (50 mg of elbasvir and 100 mg of grazoprevir) once daily. Elbasvir/grazoprevir is used alone in patients who are treatment-naive or were previously treated with peginterferon alfa and ribavirin, but is used in conjunction with ribavirin in those previously treated with peginterferon alfa, ribavirin, and an HCV protease inhibitor. (See Table 2.)

A treatment duration of 12 weeks is 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-naive or previously treated[a]	Elbasvir/grazoprevir	12 weeks
Previously treated with an HCV protease inhibitor[b]	Elbasvir/grazoprevir *with* ribavirin[c]	12 weeks

[a]Previously treated defined as patients who failed treatment with peginterferon alfa and ribavirin.

[b]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).

[c]Use weight-based ribavirin dosage in patients with creatinine clearance >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.

For the treatment of HCV genotype 4 infection in adults, the recommended dosage of elbasvir/grazoprevir is 1 tablet (50 mg of elbasvir and 100 mg of grazoprevir) once daily. Elbasvir/grazoprevir is used alone in patients who are treatment-naive, but is used in conjunction with ribavirin in those previously treated with peginterferon alfa and ribavirin. (See Table 3.)

A treatment duration of 12 weeks is recommended for treatment-naive patients, but a treatment duration of 16 weeks is recommended in patients 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-naive	Elbasvir/grazoprevir	12 weeks

[a]Previously treated defined as patients who failed treatment with peginterferon alfa and ribavirin.

[b]Use weight-based ribavirin dosage in patients with creatinine clearance >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.

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

Previously treated[a]	Elbasvir/grazoprevir *with* ribavirin[b]	16 weeks

[a]Previously treated defined as patients who failed treatment with peginterferon alfa and ribavirin.

[b]Use weight-based ribavirin dosage in patients with creatinine clearance >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 Individuals Coinfected with HIV.

For the treatment of chronic HCV genotype 1 or genotype 4 infection in adults with human immunodeficiency virus (HIV) coinfection, the same elbasvir/grazoprevir dosage and same HCV genotype-specific multiple-drug regimen and treatment duration recommended for HCV-infected patients without HIV coinfection should be used. (See Table 1, Table 2, and Table 3.)

■ Special Populations

Hepatic Impairment

Dosage adjustments of elbasvir/grazoprevir are not needed in patients with mild hepatic impairment (Child-Pugh class A).

Elbasvir/grazoprevir is contraindicated in those with moderate or severe hepatic impairment (Child-Pugh class B or C). (See Hepatic Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Renal Impairment

Dosage adjustments of elbasvir/grazoprevir are not needed in patients with mild, moderate, or severe renal impairment, including those requiring hemodialysis. (See Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Geriatric Patients

Dosage adjustments of elbasvir/grazoprevir are not needed in geriatric patients. (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Cautions

■ Contraindications

The fixed combination of elbasvir and grazoprevir (elbasvir/grazoprevir) is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B or C). (See Hepatic Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Concomitant use of elbasvir/grazoprevir with certain drugs (e.g., inhibitors of organic anion transporting polypeptides [OATP] 1B1 and 1B3, potent inducers of cytochrome P-450 [CYP] 3A, efavirenz) is contraindicated. (See Drug Interactions.)

When elbasvir/grazoprevir is used in conjunction *with* ribavirin, the contraindications for ribavirin apply. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions: Warnings/Precautions.)

■ Warnings/Precautions

Hepatic Effects

In clinical trials evaluating elbasvir/grazoprevir with or without ribavirin, increased ALT concentrations (exceeding 5 times the upper limit of normal [ULN]) were reported in 1% of patients, usually at 8 weeks or longer after initiation of treatment (mean onset 10 weeks; range 6–12 weeks). ALT elevations usually were asymptomatic and resolved with ongoing treatment or completion of treatment. Increased rates of late-onset ALT elevations were reported in patients with increased grazoprevir plasma concentrations and in certain patient groups (e.g., 65 years of age or older, Asian descent, females). The incidence of late-onset ALT elevations did not appear to be affected by presence of cirrhosis or treatment duration.

In clinical trials, increased bilirubin concentrations (exceeding 2.5 times the ULN) were reported in 6% of patients receiving elbasvir/grazoprevir in conjunction *with* ribavirin compared with less than 1% of patients receiving elbasvir/grazoprevir alone. These bilirubin increases were predominately indirect bilirubin and typically were not associated with increased ALT concentrations.

Hepatic laboratory testing should be performed prior to initiation of elbasvir/grazoprevir, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of elbasvir/grazoprevir treatment, additional hepatic laboratory testing should be performed at treatment week 12.

If ALT concentrations remain persistently greater than 10 times the ULN, discontinuance of elbasvir/grazoprevir should be considered. If ALT elevations are accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR), the drug should be discontinued. Patients should be advised to immediately contact a clinician if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces.

Interactions

Concomitant use of elbasvir/grazoprevir and certain drugs is contraindicated or not recommended. Concomitant use with some drugs may result in drug interactions leading to loss of therapeutic effect and possible development of resistance to elbasvir/grazoprevir. Certain other drug interactions may result in clinically important adverse reactions due to increased exposures of the concomitant drugs or components of elbasvir/grazoprevir.

Potential drug interactions should be considered prior to and during elbasvir/grazoprevir treatment. Drugs used concomitantly with elbasvir/grazoprevir should be reviewed during the course of treatment and the patient should be monitored for adverse reactions associated with these drugs. (See Drug Interactions.)

Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens

When elbasvir/grazoprevir is used, the cautions, precautions, contraindications, and drug interactions associated with both drugs in the fixed combination must be considered. Cautionary information applicable to specific populations (e.g., pregnant or nursing women, individuals with hepatic or renal impairment, geriatric patients) should be considered for each drug.

When elbasvir/grazoprevir is used in conjunction *with* ribavirin, the cautions, precautions, and contraindications associated with ribavirin also should be considered. (See Cautions in Ribavirin 8:18.32.) Ribavirin may cause fetal toxicity and/or death and extreme care *must* be taken to avoid pregnancy in female patients and in female partners of male patients receiving ribavirin-containing regimens. Women of childbearing potential should have a negative pregnancy test immediately prior to initiating ribavirin and pregnancy tests should be performed 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. (See Cautions: Pregnancy, Fertility, and Lactation, in Ribavirin 8:18.32.)

Specific Populations

Pregnancy.

Adequate data are not available regarding use of elbasvir/grazoprevir in pregnant women. Animal reproduction studies using elbasvir or grazoprevir have not revealed evidence of fetal harm at exposures greater than those attained with recommended human dosage.

When elbasvir/grazoprevir is used in conjunction *with* ribavirin, clinicians should consider that ribavirin may cause fetal toxicity and/or death and extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients receiving the ribavirin-containing regimen. (See Cautions: Pregnancy, Fertility, and Lactation, in Ribavirin 8:18.32.)

Lactation.

It is not known whether elbasvir/grazoprevir is distributed into human milk, affects human milk production, or affects the breast-fed infant. Both elbasvir and grazoprevir are distributed into milk in rats.

The benefits of breast-feeding and the importance of elbasvir/grazoprevir to the woman should be considered along with the potential adverse effects on the breast-fed child from the drug or from the underlying maternal condition.

When elbasvir/grazoprevir is used in conjunction *with* ribavirin, the potential for adverse reactions to ribavirin in nursing infants should be considered and a decision should be made whether to discontinue nursing or the ribavirin-containing regimen, taking into account the importance of the treatment regimen to the woman. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions: Warnings/Precautions.)

Pediatric Use.

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

Pharmacokinetics of elbasvir/grazoprevir have not been evaluated in pediatric patients.

Geriatric Use.

In clinical trials, a higher rate of late-onset ALT elevations was reported in individuals 65 years of age and older. (See Hepatic Effects under Cautions: Warnings/Precautions.)

In population pharmacokinetic analyses, the areas under the plasma concentration-time curves (AUCs) of elbasvir and grazoprevir are estimated to be increased by 16 and 45%, respectively, in individuals 65 years of age and older compared with AUCs in younger adults.

Hepatic Impairment.

Elbasvir/grazoprevir is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) because increased grazoprevir plasma concentrations are expected and the risk of ALT elevations is increased in these patients. Data are insufficient regarding efficacy and safety of elbasvir/grazoprevir in HCV-infected patients with moderate hepatic function.

Efficacy and safety of elbasvir/grazoprevir have not been established in liver transplant recipients or pretransplant patients.

In population pharmacokinetic analyses of elbasvir and grazoprevir in adults with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C) without HCV infection, the AUC of grazoprevir is increased by 1.7-, 5-, and 12-fold, respectively, compared with AUCs reported in adults with normal hepatic function.

There are no clinically important differences in the AUCs of elbasvir in adults with mild, moderate, or severe hepatic impairment compared with AUCs reported in adults with normal hepatic function.

Although elbasvir AUCs in HCV-infected adults with compensated cirrhosis are similar to those reported in HCV-infected adults without cirrhosis, grazoprevir AUCs in HCV-infected adults with compensated cirrhosis are 1.65-fold higher than those reported in HCV-infected adults without cirrhosis.

Renal Impairment.

In population pharmacokinetic analyses of elbasvir and grazoprevir in adults with severe renal impairment (not dependent on dialysis) and adults requiring hemodialysis, the AUC of elbasvir was increased by 46 and 25%, respectively, and the AUC of grazoprevir was increased by 40 and 10%, respectively, compared with adults without severe renal impairment. These changes in elbasvir and grazoprevir exposures in HCV-infected adults with renal impairment (with or without hemodialysis) are not considered clinically important.

Elbasvir and grazoprevir are not removed by hemodialysis; the drugs are unlikely to be removed by peritoneal dialysis since they are highly bound to plasma proteins.

Race.

In clinical trials, a higher rate of late-onset ALT elevations was observed in Asians. (See Hepatic Effects under Cautions: Warnings/Precautions.) In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs were estimated to be increased by 15 and 50%, respectively, in Asians compared with AUCs reported in Caucasians; dosage adjustments are not needed based on race.

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

Gender.

In clinical trials, a higher rate of late-onset ALT elevations was observed in females. (See Hepatic Effects under Cautions: Warnings/Precautions.)

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs were estimated to be increased by 50 and 30%, respectively, in females compared with AUCs reported in males; dosage adjustments are not needed based on gender.

■ Common Adverse Effects

Elbasvir/grazoprevir: Adverse effects reported in 5% or more of patients include fatigue, headache, insomnia, dizziness, nausea, diarrhea, upper respiratory tract infection, and arthralgia.

Elbasvir/grazoprevir in conjunction *with* ribavirin: Adverse effects reported in 5% or more of patients include fatigue, headache, asthenia, nausea, vomiting, diarrhea, constipation, upper abdominal pain, insomnia, anemia, decreased hemoglobin concentrations, elevated total bilirubin concentrations, and elevated triacylglycerol lipase concentrations.

Drug Interactions

The following drug interactions are based on studies that used the fixed combination of elbasvir and grazoprevir (elbasvir/grazoprevir), elbasvir alone, or grazoprevir alone, or are predicted drug interactions that may occur with elbasvir/grazoprevir. When elbasvir/grazoprevir is used, interactions associated with both drugs in the fixed combination should be considered.

■ Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes

Elbasvir and grazoprevir are both substrates of cytochrome P-450 (CYP) isoenzyme 3A. Elbasvir does not inhibit CYP3A in vitro; grazoprevir is a weak inhibitor of CYP3A in vivo.

Pharmacokinetic interactions are possible if elbasvir/grazoprevir is used concomitantly with moderate or potent inducers of CYP3A (decreased elbasvir and grazoprevir concentrations and possible loss of therapeutic effect) or potent inhibitors of CYP3A (increased elbasvir and grazoprevir concentrations).

Concomitant use of elbasvir/grazoprevir and potent CYP3A inducers is contraindicated and concomitant use with moderate CYP3A inducers is not recommended. Concomitant use of elbasvir/grazoprevir and certain potent CYP3A inhibitors is not recommended.

In vitro, elbasvir and grazoprevir both inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6. However, clinically important pharmacokinetic interactions are not expected if elbasvir/grazoprevir is used concomitantly with substrates of these CYP isoenzymes. Based on in vitro data, it is unlikely that administration of multiple doses of elbasvir or grazoprevir would induce metabolism of drugs metabolized by CYP1A2, 2B6, or 3A.

■ Drugs Affecting or Affected by P-glycoprotein Transport

Elbasvir and grazoprevir are both substrates of P-glycoprotein (P-gp) transport; the role of intestinal P-gp in absorption of elbasvir and grazoprevir appears to be minimal.

In vitro, elbasvir inhibits P-gp; grazoprevir is not an inhibitor of P-gp.

■ Drugs Affecting or Affected by Breast Cancer Resistance Protein

Elbasvir and grazoprevir are both inhibitors of intestinal breast cancer resistance protein (BCRP). Concomitant use of elbasvir/grazoprevir and drugs that are BCRP substrates may result in increased concentrations of such substrate drugs.

■ Drugs Affecting or Affected by Organic Anion Transport Polypeptides

Grazoprevir is a substrate and inhibitor of organic anion transporting polypeptide (OATP) 1B1 and 1B3. Elbasvir is not a substrate of OATP1B.

Pharmacokinetic interactions are possible if elbasvir/grazoprevir is used concomitantly with OATP1B1 or 1B3 inhibitors (increased grazoprevir concentrations). Concomitant use of elbasvir/grazoprevir and OATP1B1 or 1B3 inhibitors is contraindicated.

■ Drugs Affecting or Affected by Other Enzymes

In vitro, elbasvir and grazoprevir do not inhibit carboxylesterase (CES) 1, CES2, cathepsin A (CatA), or uridine diphosphate-glucuronosyl transferase (UGT) 1A1. Clinically important pharmacokinetic interactions are not expected if elbasvir/grazoprevir is used concomitantly with CES1, CES2, CatA, or UGT1A1 substrates.

■ Drugs Affecting Gastric pH

Antacids

Dosage adjustments are not needed if antacids are used concomitantly with elbasvir/grazoprevir.

Histamine H_2-receptor Antagonists

Concomitant use of famotidine and elbasvir/grazoprevir does not result in clinically important changes in the pharmacokinetics of elbasvir or grazoprevir.

Dosage adjustments are not needed if a histamine H_2-receptor antagonist is used concomitantly with elbasvir/grazoprevir.

Proton-pump Inhibitors

Concomitant use of pantoprazole and elbasvir/grazoprevir does not result in clinically important changes in the pharmacokinetics of elbasvir or grazoprevir.

Dosage adjustments are not needed if a proton-pump inhibitor is used concomitantly with elbasvir/grazoprevir.

■ Antibacterial Agents

Penicillins

Nafcillin.

Concomitant use of nafcillin and elbasvir/grazoprevir may result in decreased elbasvir and grazoprevir concentrations due to moderate CYP3A induction by nafcillin, which may lead to reduced therapeutic effect of the HCV antiviral.

Concomitant use of nafcillin and elbasvir/grazoprevir is not recommended.

■ Anticonvulsants

Carbamazepine

Concomitant use of carbamazepine and elbasvir/grazoprevir may result in substantially decreased elbasvir and grazoprevir concentrations due to potent CYP3A induction by carbamazepine, which may lead to loss of virologic response to the HCV antiviral.

Concomitant use of carbamazepine and elbasvir/grazoprevir is contraindicated.

Phenytoin

Concomitant use of phenytoin and elbasvir/grazoprevir may result in substantially decreased elbasvir and grazoprevir concentrations due to potent CYP3A induction by phenytoin, which may lead to loss of virologic response to the HCV antiviral.

Concomitant use of phenytoin and elbasvir/grazoprevir is contraindicated.

■ Antifungal Agents

Ketoconazole

In healthy adults, concomitant use of ketoconazole (400 mg once daily) and elbasvir (single 50-mg dose) or grazoprevir (single 100-mg dose) results in increased plasma concentrations and areas under the plasma concentration-time curves (AUCs) of elbasvir and grazoprevir, which may increase the overall risk of hepatotoxicity.

Concomitant use of ketoconazole and elbasvir/grazoprevir is not recommended.

■ Antimycobacterial Agents

Rifampin

Concomitant use of rifampin (single 600-mg oral or IV dose) and elbasvir (single 50-mg dose) results in slightly increased elbasvir plasma concentrations and AUC. Although specific studies are not available, concomitant use of multiple doses of rifampin and elbasvir is expected to result in clinically important decreases in elbasvir plasma concentrations because of potent CYP3A induction and may lead to loss of virologic response to the HCV antiviral.

Concomitant use of rifampin (single 600-mg oral or IV dose) and grazoprevir (single 200-mg dose) results in substantially increased grazoprevir plasma concentrations and AUC, presumably due to OATP1B1 inhibition by rifampin. However, concomitant use of multiple doses of rifampin and grazoprevir results in clinically important decreases in grazoprevir concentrations, most likely because of the mixed effects of rifampin on OATP1B (inhibition) and CYP3A4 (induction) and may lead to loss of virologic response to the HCV antiviral.

Concomitant use of rifampin and elbasvir/grazoprevir is contraindicated.

■ Antiretroviral Agents

HIV Integrase Inhibitors (INSTIs)

Dolutegravir.

Concomitant use of dolutegravir and elbasvir/grazoprevir does not result in clinically important changes in the pharmacokinetics of elbasvir, grazoprevir, or dolutegravir. Dosage adjustments are not needed.

Elvitegravir.

Concomitant use of the fixed combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (EVG/c/FTC/TDF) or the fixed combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (EVG/c/FTC/TAF) and elbasvir/grazoprevir may result in increased elbasvir and grazoprevir concentrations.

Concomitant use of EVG/c/FTC/TDF or EVG/c/FTC/TAF and elbasvir/grazoprevir is not recommended.

Raltegravir.

Concomitant use of raltegravir and elbasvir/grazoprevir does not result in clinically important changes in the pharmacokinetics of elbasvir, grazoprevir, or raltegravir. Dosage adjustments are not needed.

HIV Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Efavirenz.

Concomitant use of efavirenz (600 mg once daily) and elbasvir (50 mg once daily) or grazoprevir (200 mg once daily) results in substantially decreased elbasvir or grazoprevir concentrations due to potent CYP3A induction by efavirenz, which may lead to loss of virologic response to the HCV antiviral.

Concomitant use of efavirenz and elbasvir/grazoprevir is contraindicated.

Etravirine.

Concomitant use of etravirine and elbasvir/grazoprevir may result in decreased elbasvir and grazoprevir concentrations due to moderate CYP3A induction by etravirine, which may lead to reduced therapeutic effect of the HCV antiviral.

Concomitant use of etravirine and elbasvir/grazoprevir is not recommended.

Rilpivirine.

Concomitant use of rilpivirine and elbasvir/grazoprevir does not result in clinically important changes in the pharmacokinetics of elbasvir, grazoprevir, or rilpivirine. Dosage adjustments are not needed.

HIV Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Abacavir.

Clinically important pharmacokinetic interactions are not expected if abacavir is used concomitantly with elbasvir/grazoprevir.

Emtricitabine.

Clinically important pharmacokinetic interactions are not expected if emtricitabine is used concomitantly with elbasvir/grazoprevir.

Lamivudine.

Clinically important pharmacokinetic interactions are not expected if lamivudine is used concomitantly with elbasvir/grazoprevir.

Tenofovir.

Concomitant use of tenofovir disoproxil fumarate (tenofovir DF) and elbasvir or grazoprevir does not result in clinically important changes in the pharmacokinetics of elbasvir, grazoprevir, or tenofovir. Dosage adjustments are not needed.

HIV Protease Inhibitors (PIs)

Atazanavir.

Concomitant use of *ritonavir-boosted* atazanavir (300 mg of atazanavir and 100 mg of ritonavir once daily) and elbasvir (50 mg once daily) results in increased elbasvir concentrations. Concomitant use of *ritonavir-boosted* atazanavir (300 mg of atazanavir and 100 mg of ritonavir once daily) and grazoprevir (200 mg once daily) results in substantially increased grazoprevir concentrations due to OATP1B1 and 1B3 inhibition by *ritonavir-boosted* atazanavir. Increased grazoprevir concentrations may increase the risk of ALT elevations.

Concomitant use of atazanavir and elbasvir/grazoprevir is contraindicated.

Darunavir.

Concomitant use of *ritonavir-boosted* darunavir (600 mg of darunavir and 100 mg of ritonavir twice daily) and elbasvir (50 mg once daily) results in increased elbasvir concentrations. Concomitant use of *ritonavir-boosted* darunavir (600 mg of darunavir and 100 mg of ritonavir twice daily) and grazoprevir (200 mg once daily) results in substantially increased grazoprevir concentrations due to OATP1B1 and 1B3 inhibition by *ritonavir-boosted* darunavir. Increased grazoprevir concentrations may increase the risk of ALT elevations.

Concomitant use of darunavir and elbasvir/grazoprevir is contraindicated.

Lopinavir.

Concomitant use of the fixed combination of lopinavir and ritonavir (lopinavir/ritonavir) and elbasvir (50 mg once daily) results in increased elbasvir concentrations. Concomitant use of lopinavir/ritonavir and grazoprevir (200 mg once daily) results in substantially increased grazoprevir concentrations due to OATP1B1 and 1B3 inhibition by lopinavir/ritonavir. Increased grazoprevir concentrations may increase the risk of ALT elevations.

Concomitant use of lopinavir and elbasvir/grazoprevir is contraindicated.

Ritonavir.

Concomitant use of ritonavir (100 mg twice daily) and grazoprevir (single 200-mg dose) results in increased grazoprevir concentrations.

Saquinavir.

Pharmacokinetic interactions are expected if saquinavir and elbasvir/grazoprevir are used concomitantly (substantially increased grazoprevir concentrations due to potent OATP1B1 and 1B3 inhibition by saquinavir). Increased grazoprevir concentrations may increase the risk of ALT elevations.

Concomitant use of saquinavir and elbasvir/grazoprevir is contraindicated.

Tipranavir.

Pharmacokinetic interactions are expected if tipranavir and elbasvir/grazoprevir are used concomitantly (substantially increased grazoprevir concentrations due to potent OATP1B1 and 1B3 inhibition by tipranavir). Increased grazoprevir concentrations may increase the risk of ALT elevations.

Concomitant use of tipranavir and elbasvir/grazoprevir is contraindicated.

■ Benzodiazepines

Midazolam

Concomitant use of midazolam (single 2-mg dose) and grazoprevir (200 mg once daily) results in a 34% increase in midazolam exposures due to weak CYP3A inhibition by grazoprevir.

■ Bosentan

Possible pharmacokinetic interactions if bosentan and elbasvir/grazoprevir are used concomitantly (decreased elbasvir and grazoprevir concentrations due to moderate CYP3A induction by bosentan, which may lead to reduced therapeutic effect of the HCV antiviral).

Concomitant use of bosentan and elbasvir/grazoprevir is not recommended.

■ Cardiac Agents

Digoxin

Concomitant use of digoxin (single 0.25-mg dose) and elbasvir (50 mg once daily) does not result in clinically important changes in digoxin plasma concentrations or AUC.

Dosage adjustments are not needed if digoxin is used concomitantly with elbasvir/grazoprevir.

■ Corticosteroids

Prednisone

Concomitant use of prednisone and elbasvir/grazoprevir does not result in clinically important changes in the pharmacokinetics of elbasvir, grazoprevir, or prednisone. Dosage adjustments are not needed.

■ Entecavir

Clinically important pharmacokinetic interactions are not expected if entecavir is used concomitantly with elbasvir/grazoprevir.

■ Estrogens and Progestins

Concomitant use of elbasvir or grazoprevir with an oral contraceptive containing ethinyl estradiol and levonorgestrel does not result in clinically important changes in the pharmacokinetics of ethinyl estradiol or levonorgestrel. Dosage adjustments are not needed.

■ HCV Antivirals

HCV Polymerase Inhibitors

Sofosbuvir.

Concomitant use of sofosbuvir and elbasvir/grazoprevir does not result in clinically important pharmacokinetic interactions. Dosage adjustments are not needed.

■ HMG-CoA Reductase Inhibitors

Atorvastatin

Concomitant use of atorvastatin (single 10-mg dose) and elbasvir (50 mg once daily) in conjunction with grazoprevir (200 mg once daily) results in increased atorvastatin plasma concentrations and AUC.

If atorvastatin is used concomitantly with elbasvir/grazoprevir, atorvastatin dosage should not exceed 20 mg once daily.

Fluvastatin

Possible pharmacokinetic interaction if fluvastatin and elbasvir/grazoprevir are used concomitantly (increased fluvastatin concentrations).

If fluvastatin and elbasvir/grazoprevir are used concomitantly, the lowest necessary dosage of fluvastatin should be used and the patient should be closely monitored for statin-associated adverse effects (e.g., myopathy).

Lovastatin

Possible pharmacokinetic interaction if lovastatin and elbasvir/grazoprevir are used concomitantly (increased lovastatin concentrations).

If lovastatin and elbasvir/grazoprevir are used concomitantly, the lowest necessary dosage of lovastatin should be used and the patient should be closely monitored for statin-associated adverse effects (e.g., myopathy).

Pitavastatin

Concomitant use of pitavastatin (single 1-mg dose) and grazoprevir (200 mg once daily) and does not have a clinically important effect on the pharmacokinetics of pitavastatin. Dosage adjustments are not needed.

Pravastatin

Concomitant use of pravastatin (single 40-mg dose) and elbasvir (50 mg once daily) in conjunction with grazoprevir (200 mg once daily) does not have a clinically important effect on the pharmacokinetics of pravastatin. Dosage adjustments are not needed.

Rosuvastatin

Concomitant use of rosuvastatin (single 10-mg dose) and elbasvir (50 mg once daily) in conjunction with grazoprevir (200 mg once daily) results in increased rosuvastatin plasma concentrations and AUC.

If rosuvastatin is used concomitantly with elbasvir/grazoprevir, rosuvastatin dosage should not exceed 10 mg once daily.

Simvastatin

Possible pharmacokinetic interaction if simvastatin and elbasvir/grazoprevir are used concomitantly (increased simvastatin concentrations).

If simvastatin and elbasvir/grazoprevir are used concomitantly, the lowest necessary dosage of simvastatin should be used and the patient should be closely monitored for statin-associated adverse effects (e.g., myopathy).

■ Immunosuppressive Agents

Cyclosporine

Concomitant use of cyclosporine (single 400-mg dose) and elbasvir (50 mg once daily) in conjunction with grazoprevir (200 mg once daily) results in increased elbasvir plasma concentrations and AUC and substantially increased grazoprevir plasma concentrations and AUC. Substantially increased grazoprevir concentrations are caused by OATP1B1 and 1B3 inhibition by cyclosporine and may increase the risk of ALT elevations.

Concomitant use of cyclosporine and elbasvir/grazoprevir is contraindicated.

Tacrolimus

Concomitant use of tacrolimus (single 2-mg dose) and elbasvir (50 mg once daily) in conjunction with grazoprevir (200 mg once daily) results in a 43% increase in tacrolimus exposures due to weak CYP3A inhibition by grazoprevir; elbasvir and grazoprevir concentrations are not affected.

If tacrolimus and elbasvir/grazoprevir are used concomitantly, tacrolimus whole blood concentrations, renal function, and tacrolimus-associated adverse effects should be monitored frequently.

■ Modafinil

Possible pharmacokinetic interactions if modafinil and elbasvir/grazoprevir are used concomitantly (decreased elbasvir and grazoprevir concentrations due to moderate CYP3A induction by modafinil, which may lead to reduced therapeutic effect of the HCV antiviral).

Concomitant use of modafinil and elbasvir/grazoprevir is not recommended.

■ Montelukast

Concomitant use of montelukast and grazoprevir does not result in clinically important changes in the pharmacokinetics of montelukast.

■ Mycophenolate

Concomitant use of mycophenolate mofetil and elbasvir in conjunction with grazoprevir does not result in clinically important changes in elbasvir, grazoprevir, or mycophenolic acid plasma concentrations or AUC. Dosage adjustments are not needed.

■ Opiate Agonists and Opiate Partial Agonists

Buprenorphine

Concomitant use of the fixed combination of buprenorphine and naloxone (buprenorphine/naloxone) and elbasvir does not result in clinically important effects on plasma concentrations or AUCs of elbasvir or buprenorphine. Concomitant use of buprenorphine/naloxone and grazoprevir does not result in clinically important effects on plasma concentrations or AUC of buprenorphine. Dosage adjustments are not needed.

Methadone

Concomitant use of methadone does not result in clinically important effects on plasma concentrations or AUCs of elbasvir or grazoprevir. Dosage adjustments are not needed.

■ Phosphate Binders

Concomitant use of sevelamer carbonate or calcium acetate and elbasvir/grazoprevir does not result in clinically important changes in the pharmacokinetics of elbasvir or grazoprevir.

Dosage adjustments are not needed if elbasvir/grazoprevir is used concomitantly with phosphate binders.

■ Ribavirin

Concomitant use of ribavirin and elbasvir/grazoprevir does not have clinically important effects on peak plasma concentrations or AUCs of elbasvir or grazoprevir compared with administration of elbasvir/grazoprevir alone. Dosage adjustments are not needed if elbasvir/grazoprevir is used in conjunction with ribavirin.

There was no in vitro evidence of antagonistic anti-HCV effects between ribavirin and elbasvir or ribavirin and grazoprevir when the combinations were evaluated in HCV replicon studies.

■ St. John's Wort

Concomitant use of St. John's wort (*Hypericum perforatum*) and elbasvir/grazoprevir may result in substantially decreased elbasvir and grazoprevir concentrations due to potent CYP3A induction by St. John's wort, which may lead to loss of virologic response to the HCV antiviral.

Concomitant use of St. John's wort and elbasvir/grazoprevir is contraindicated.

Description

Elbasvir and grazoprevir (elbasvir/grazoprevir) is a fixed combination containing 2 hepatitis C virus (HCV) antivirals. Elbasvir is an HCV nonstructural 5A (NS5A) replication complex inhibitor (NS5A inhibitor). Grazoprevir is an HCV nonstructural 3/4A (NS3/4A) protease inhibitor. Both drugs are direct-acting antivirals (DAAs) with activity against HCV. There was no in vitro evidence of antagonistic anti-HCV effects between elbasvir and grazoprevir when the combination was evaluated 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 that 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 that grazoprevir has activity against HCV genotypes 1a, 1b, and 4.

Certain amino acid substitutions in NS5A of HCV genotypes 1a, 1b, and 4 have been selected in cell culture and have been associated with reduced susceptibility to elbasvir in vitro in replicon studies. In HCV genotype 1a replicons, single M28A/G/T, Q30D/E/H/K/R, L31M/V, H28D, and Y93C/H/N substitutions in NS5A are associated with reduced susceptibility to elbasvir (up to 2000-fold lower); in HCV genotype 1b replicons, single L28M, L31F, and Y93H substitutions in NS5A are associated with reduced susceptibility to elbasvir (up to17-fold lower). In HCV genotype 4 replicons, single L30S, M31V, and Y93H substitutions in NS5A are associated with reduced susceptibility to elbasvir (up to 23-fold lower). 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 have been selected in cell culture and have been associated with reduced susceptibility to grazoprevir in vitro in replicon studies. In HCV genotype 1a replicons, single Y56H, R155K, A156G/T/V, and D168A/E/G/N/S/V/Y substitutions in NS3 are associated with reduced susceptibility to grazoprevir (up to 81-fold lower); in HCV genotype 1b replicons, single F43S, Y56F, V107I, A156S/T/V, and D168A/G/V substitutions in NS3 are associated with reduced susceptibility to grazoprevir (up to 375-fold lower). In HCV genotype 4 replicons, single D168A/V substitutions in NS3 are associated with reduced susceptibility to grazoprevir (up to 320-fold lower). 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.

Cross-resistance among HCV NS5A inhibitors and among HCV NS3/4A protease inhibitors is possible. Efficacy of elbasvir/grazoprevir has not been established in patients in whom previous treatment with a regimen that included an HCV NS5A inhibitor failed. Only limited data are available regarding efficacy of elbasvir/grazoprevir in patients who previously failed 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 are active against HCV with amino acid substitutions associated with resistance to HCV NS5B polymerase inhibitors.

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. Although not considered clinically important, administration of elbasvir/grazoprevir with a high-fat meal (approximately 900 kcal, 500 kcal from fat) in healthy adults decreases the area under the plasma concentration-time curve (AUC) and peak plasma concentrations of elbasvir by approximately 11 and 15%, respectively, and increases the AUC and peak plasma concentrations of

grazoprevir by approximately 1.5- and 2.8-fold, respectively, relative to administration in the fasting state. When a once-daily regimen of elbasvir/grazoprevir is used, steady-state concentrations of elbasvir and grazoprevir are attained within approximately 6 days. Concomitant use of elbasvir and grazoprevir does not have a clinically important effect on the pharmacokinetics of either drug compared with administration alone.

Elbasvir pharmacokinetics are similar in healthy and HCV-infected adults; elbasvir exposures increase in a dose-proportional manner over the dosage range of 5–200 mg once daily. Grazoprevir exposures are 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 that peak plasma concentrations and AUC increase in a more-than-dose-proportional manner. Preclinical studies indicate that elbasvir is distributed into most tissues (including the liver) and grazoprevir is distributed principally into the liver, which is likely facilitated by active transport of the drug through organic anion transporting polypeptide (OATP) 1B1 and 1B3 liver uptake transporters. Elbasvir and grazoprevir are both partially eliminated by oxidative metabolism, principally by cytochrome P-450 (CYP) 3A; both drugs are extensively (99.9 and 98.8%, respectively) bound to plasma proteins (e.g., serum albumin, α_1-acid glycoprotein). Both elbasvir and grazoprevir are eliminated principally in feces. Over 90% of each dose is excreted in feces and less than 1% is excreted in urine. In HCV-infected adults, the geometric mean apparent terminal half-lives of elbasvir and grazoprevir are approximately 24 and 31 hours, respectively.

Advice to Patients

Advise patients that the fixed-combination preparation of elbasvir and grazoprevir (elbasvir/grazoprevir) should be taken once daily (with or without food) on a regular dosing schedule.

Advise patients that elbasvir/grazoprevir should be stored 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 a 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: Warnings/Precautions.)

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

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®**, Merck