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## FULL PRESCRIBING INFORMATION

### **WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV**

**Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with ZEPATIER. HBV reactivation has been reported in HCV/HBV coinfecting patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfecting patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated [see *Warnings and Precautions (5.1)*].**

## **1 INDICATIONS AND USAGE**

ZEPATIER® is indicated for the treatment of chronic hepatitis C virus (HCV) genotype 1 or 4 infection in adult and pediatric patients 12 years of age and older or weighing at least 30 kg.

ZEPATIER is indicated for use with ribavirin in certain patient populations [see *Dosage and Administration (2.2)*].

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Testing Prior to the Initiation of Therapy**

#### Testing for HBV Infection

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with ZEPATIER [see *Warnings and Precautions (5.1)*].

#### NS5A Resistance Testing in HCV Genotype 1a-Infected Patients

Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with ZEPATIER to determine dosage regimen and duration [see *Dosage and Administration (2.2)*], *Table 1*. In subjects receiving ZEPATIER for 12 weeks, sustained virologic response (SVR12) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93 [see *Microbiology (12.4)*], *Table 12*.

#### Hepatic Laboratory Testing

Obtain hepatic laboratory testing prior to and during treatment with ZEPATIER [see *Warnings and Precautions (5.2, 5.3)*].

### **2.2 Recommended Dosage in Adult and Pediatric Patients 12 Years of Age and Older or Weighing at Least 30 kg**

ZEPATIER is a two-drug, fixed-dose combination product containing 50 mg of elbasvir and 100 mg of grazoprevir in a single tablet. The recommended dosage of ZEPATIER is one tablet taken orally once daily with or without food [see *Clinical Pharmacology (12.3)*]. ZEPATIER is used in combination with ribavirin in certain patient populations (see *Table 1*). When administered with ZEPATIER, the recommended dosage of ribavirin in patients without renal impairment is weight-based administered in two divided doses with food. For further information on ribavirin dosing and dosage modifications, refer to the ribavirin prescribing information.

#### Treatment Regimen and Duration of Therapy

Relapse rates are affected by baseline host and viral factors and differ between treatment regimens and durations for certain subgroups [see *Clinical Studies (14)*].

*Table 1* below provides the recommended ZEPATIER treatment regimen and duration based on the patient population and genotype in HCV mono-infected and HCV/HIV-1 co-infected patients with or without cirrhosis and with or without renal impairment including patients receiving hemodialysis.

**Table 1: Recommended Dosage Regimens and Durations for ZEPATIER for Treatment of HCV Genotype 1 or 4 in Patients with or without Cirrhosis**

| Patient Population   | Treatment                   | Duration |
|--|-----------------------------|----------|
| Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms <sup>†</sup> | ZEPATIER                    | 12 weeks |
| Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms <sup>†</sup>    | ZEPATIER + RBV <sup>‡</sup> | 16 weeks |
| Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*  | ZEPATIER                    | 12 weeks |
| Genotype 1a <sup>§</sup> or 1b: PegIFN/RBV/PI-experienced <sup>¶</sup>                                   | ZEPATIER + RBV <sup>‡</sup> | 12 weeks |
| Genotype 4: Treatment-Naïve  | ZEPATIER                    | 12 weeks |
| Genotype 4: PegIFN/RBV-experienced*  | ZEPATIER + RBV <sup>‡</sup> | 16 weeks |

\*Patients who have failed treatment with peginterferon alfa (PegIFN) + ribavirin (RBV).

<sup>†</sup>NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93. See section 2.1 Testing prior to the initiation of therapy, subsection NS5A resistance testing in HCV genotype 1a-infected patients.

<sup>‡</sup>For patients with CrCl greater than 50 mL per minute, the recommended dosage of ribavirin is weight-based (less than 66 kg = 800 mg per day, 66 to 80 kg = 1000 mg per day, 81 to 105 kg = 1200 mg per day, greater than 105 kg = 1400 mg per day) administered in two divided doses with food. For patients with CrCl less than or equal to 50 mL per minute, including patients receiving hemodialysis, refer to the ribavirin tablet prescribing information for the correct ribavirin dosage.

In pediatric patients, the dosing for ribavirin is weight-based in two divided doses. Refer to the ribavirin tablet prescribing information for the correct ribavirin dosage regimen.

<sup>§</sup>The optimal ZEPATIER-based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established.

<sup>¶</sup>Patients who have failed treatment with PegIFN + RBV + HCV NS3/4A protease inhibitor (PI): boceprevir, simeprevir, or telaprevir.

## 2.3 Renal Impairment

No dosage adjustment of ZEPATIER is recommended in patients with any degree of renal impairment including patients on hemodialysis. Administer ZEPATIER with or without ribavirin according to the recommendations in Table 1 [see *Use in Specific Populations (8.8) and Clinical Studies (14.4)*]. Refer to the ribavirin tablet prescribing information for the correct ribavirin dosage for patients with CrCl less than or equal to 50 mL per minute.

## 2.4 Hepatic Impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation [see *Contraindications (4), Warnings and Precautions (5.3), Use in Specific Populations (8.9), and Clinical Pharmacology (12.3)*].

## 3 DOSAGE FORMS AND STRENGTHS

ZEPATIER is available as a beige-colored, oval-shaped, film-coated tablet debossed with “770” on one side and plain on the other. Each tablet contains 50 mg elbasvir and 100 mg grazoprevir.

## 4 CONTRAINDICATIONS

- ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of alanine aminotransferase (ALT) elevations [see *Warnings and Precautions (5.2), Use in Specific Populations (8.9), and Clinical Pharmacology (12.3)*].

- ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of hepatic decompensation due to the risk of hepatic decompensation [see *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.9)*].
- ZEPATIER is contraindicated with inhibitors of organic anion transporting polypeptides 1B1/3 (OATP1B1/3) that are known or expected to significantly increase grazoprevir plasma concentrations, strong inducers of cytochrome P450 3A (CYP3A), and efavirenz [see *Warnings and Precautions (5.5)*, *Drug Interactions (7)*, and *Clinical Pharmacology (12.3)*].
- If ZEPATIER is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.

Table 2 lists drugs that are contraindicated with ZEPATIER.

**Table 2: Drugs that are Contraindicated with ZEPATIER**

| <b>Drug Class</b>  | <b>Drug(s) within Class that are Contraindicated</b>             | <b>Clinical Comment*</b>  |
|--------------------|--|---|
| Anticonvulsants    | Phenytoin<br>Carbamazepine                                       | May lead to loss of virologic response to ZEPATIER due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction. |
| Antimycobacterials | Rifampin   | May lead to loss of virologic response to ZEPATIER due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction. |
| Herbal Products    | St. John's Wort (Hypericum perforatum)                           | May lead to loss of virologic response to ZEPATIER due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction. |
| HIV Medications    | Efavirenz <sup>†</sup>   | May lead to loss of virologic response to ZEPATIER due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A induction.        |
| HIV Medications    | Atazanavir<br>Darunavir<br>Lopinavir<br>Saquinavir<br>Tipranavir | May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.                          |
| Immunosuppressants | Cyclosporine   | May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.                          |

\*This table is not a comprehensive list of all drugs that strongly induce CYP3A. This table may not include all OATP1B1/3 inhibitors that significantly increase grazoprevir plasma concentrations.

<sup>†</sup>Efavirenz is included as a strong CYP3A inducer in this table, since co-administration reduced grazoprevir exposure by ≥80% [see *Table 9*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV**

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfecting patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). HBV reactivation has also been reported in

patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increases in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with ZEPATIER. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with ZEPATIER and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

## **5.2 Increased Risk of ALT Elevations**

During clinical trials with ZEPATIER with or without ribavirin, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in the following subpopulations: female sex (2% [10/608]), Asian race (2% [4/164]), and age 65 years or older (2% [3/177]) [see *Adverse Reactions (6.1)*].

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

- Patients should be instructed to consult their healthcare professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces.
- Consider discontinuing ZEPATIER if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue ZEPATIER if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or International Normalized Ratio (INR).

## **5.3 Risk of Hepatic Decompensation/Failure in Patients with Evidence of Advanced Liver Disease**

Postmarketing cases of hepatic decompensation/failure, including those with fatal outcomes, have been reported in patients treated with HCV NS3/4A protease inhibitor-containing regimens, including ZEPATIER.

Reported cases occurred in patients treated with HCV NS3/4A protease inhibitor-containing regimens with baseline cirrhosis with and without moderate or severe liver impairment (Child-Pugh B or C) as well as some patients without cirrhosis. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatic laboratory testing should be performed in all patients [see *Warnings and Precautions (5.2)*]. In patients with compensated cirrhosis (Child-Pugh A) or evidence of advanced liver disease, such as portal hypertension, more frequent hepatic laboratory testing may be warranted; and patients should be monitored for signs and symptoms of hepatic decompensation such as the presence of jaundice, ascites, hepatic encephalopathy, and variceal hemorrhage. Discontinue ZEPATIER in patients who develop evidence of hepatic decompensation/failure.

ZEPATIER is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation [see *Contraindications (4)*, *Adverse Reactions (6.1)*, *Use in Specific Populations (8.9)*, and *Clinical Pharmacology (12.3)*].

#### 5.4 Risks Associated with Ribavirin Combination Treatment

If ZEPATIER is administered with ribavirin, the warnings and precautions for ribavirin, including the pregnancy avoidance warning, also apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of warnings and precautions for ribavirin [see *Dosage and Administration (2.2)*].

#### 5.5 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of ZEPATIER and certain drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Possible clinically significant adverse reactions from greater exposure of concomitant drugs or components of ZEPATIER.
- Significant decrease of elbasvir and grazoprevir plasma concentrations which may lead to reduced therapeutic effect of ZEPATIER and possible development of resistance.

See Tables 2 and 6 for steps to prevent or manage these known or potentially significant drug interactions, including dosing recommendations [see *Contraindications (4) and Drug Interactions (7.2)*].

### 6 ADVERSE REACTIONS

The following adverse reaction is described below and elsewhere in the labeling:

- Increased Risk of ALT Elevations [see *Warnings and Precautions (5.2)*].

#### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

If ZEPATIER is administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions.

##### Clinical Trials in Adult Subjects

The safety of ZEPATIER in adult subjects was assessed based on 2 placebo-controlled trials and 7 uncontrolled Phase 2 and 3 clinical trials in approximately 1700 subjects with chronic hepatitis C virus infection with compensated liver disease (with or without cirrhosis) [see *Clinical Studies (14)*].

##### Adverse Reactions with ZEPATIER in Treatment-Naïve Subjects

C-EDGE TN was a Phase 3 randomized, double-blind, placebo-controlled trial in 421 treatment-naïve (TN) subjects with HCV infection who received ZEPATIER or placebo one tablet once daily for 12 weeks. Adverse reactions (all intensity) occurring in C-EDGE TN in at least 5% of subjects treated with ZEPATIER for 12 weeks are presented in Table 3. In subjects treated with ZEPATIER who reported an adverse reaction, 73% had adverse reactions of mild severity. The type and severity of adverse reactions in subjects with compensated cirrhosis were comparable to those seen in subjects without cirrhosis. No subjects treated with ZEPATIER or placebo had serious adverse reactions. The proportion of subjects treated with ZEPATIER or placebo who permanently discontinued treatment due to adverse reactions was 1% in each group.

**Table 3: Adverse Reactions (All Intensity) Reported in ≥5% of Treatment-Naïve Subjects with HCV Treated with ZEPATIER for 12 Weeks in C-EDGE TN**

|          | C-EDGE TN                          |                                   |
|----------|------------------------------------|-----------------------------------|
|          | ZEPATIER<br>N=316<br>%<br>12 weeks | Placebo<br>N=105<br>%<br>12 weeks |
| Fatigue  | 11%                                | 10%                               |
| Headache | 10%                                | 9%                                |

C-EDGE COINFECTION was a Phase 3 open-label trial in 218 treatment-naïve HCV/HIV co-infected subjects who received ZEPATIER one tablet once daily for 12 weeks. Adverse reactions (all intensity) reported in C-EDGE COINFECTION in at least 5% of subjects treated with ZEPATIER for 12 weeks were fatigue (7%), headache (7%), nausea (5%), insomnia (5%), and diarrhea (5%). No subjects reported serious adverse reactions or discontinued treatment due to adverse reactions. No subjects switched their antiretroviral therapy regimen due to loss of plasma HIV-1 RNA suppression. Median increase in CD4+ T-cell counts of 31 cells per mm<sup>3</sup> was observed at the end of 12 weeks of treatment.

Adverse Reactions with ZEPATIER with or without Ribavirin in Treatment-Experienced Subjects

C-EDGE TE was a Phase 3 randomized, open-label trial in treatment-experienced (TE) subjects. Adverse reactions of moderate or severe intensity reported in C-EDGE TE in at least 2% of subjects treated with ZEPATIER one tablet once daily for 12 weeks or ZEPATIER one tablet once daily with ribavirin for 16 weeks are presented in Table 4. No subjects treated with ZEPATIER without ribavirin for 12 weeks reported serious adverse reactions or discontinued treatment due to adverse reactions. The proportion of subjects treated with ZEPATIER with ribavirin for 16 weeks with serious adverse reactions was 1%. The proportion of subjects treated with ZEPATIER with ribavirin for 16 weeks who permanently discontinued treatment due to adverse reactions was 3%. The type and severity of adverse reactions in subjects with cirrhosis were comparable to those seen in subjects without cirrhosis.

**Table 4: Adverse Reactions (Moderate or Severe Intensity) Reported in ≥2% of PegIFN/RBV-Experienced Subjects with HCV Treated with ZEPATIER for 12 Weeks or ZEPATIER + Ribavirin for 16 Weeks in C-EDGE TE**

|                  | C-EDGE TE                          |  |
|------------------|------------------------------------|--|
|                  | ZEPATIER<br>N=105<br>%<br>12 weeks | ZEPATIER + Ribavirin<br>N=106<br>%<br>16 weeks |
| Anemia           | 0%                                 | 8%   |
| Headache         | 0%                                 | 6%   |
| Fatigue          | 5%                                 | 4%   |
| Dyspnea          | 0%                                 | 4%   |
| Rash or Pruritus | 0%                                 | 4%   |
| Irritability     | 1%                                 | 3%   |
| Abdominal pain   | 2%                                 | 2%   |
| Depression       | 1%                                 | 2%   |
| Arthralgia       | 0%                                 | 2%   |
| Diarrhea         | 2%                                 | 0%   |

The type and severity of adverse reactions with ZEPATIER with or without ribavirin in 10 treatment-experienced subjects with HCV/HIV co-infection were comparable to those reported in subjects without HIV co-infection. Median increase in CD4+ T-cell counts of 32 cells/mm<sup>3</sup> was observed at the end of 12 weeks of treatment with ZEPATIER alone. In subjects treated with ZEPATIER with ribavirin for 16 weeks, CD4+ T-cell counts decreased a median of 135 cells per mm<sup>3</sup> at the end of treatment. No subjects switched their antiretroviral therapy regimen due to loss of plasma HIV-1 RNA suppression. No subject experienced an AIDS-related opportunistic infection.

C-SALVAGE was a Phase 2 open-label trial in 79 PegIFN/RBV/PI-experienced subjects. Adverse reactions of moderate or severe intensity reported in C-SALVAGE in at least 2% of subjects treated with ZEPATIER once daily with ribavirin for 12 weeks were fatigue (3%) and insomnia (3%). No subjects reported serious adverse reactions or discontinued treatment due to adverse reactions.

Adverse Reactions with ZEPATIER in Subjects with Severe Renal Impairment including Subjects on Hemodialysis

The safety of elbasvir and grazoprevir in comparison to placebo in subjects with severe renal impairment (Stage 4 or Stage 5 chronic kidney disease, including subjects on hemodialysis) and chronic

hepatitis C virus infection with compensated liver disease (with or without cirrhosis) was assessed in 235 subjects (C-SURFER) [see *Clinical Studies (14.4)*]. The adverse reactions (all intensity) occurring in at least 5% of subjects treated with ZEPATIER for 12 weeks are presented in Table 5. In subjects treated with ZEPATIER who reported an adverse reaction, 76% had adverse reactions of mild severity. The proportion of subjects treated with ZEPATIER or placebo with serious adverse reactions was less than 1% in each treatment arm, and less than 1% and 3% of subjects, respectively, permanently discontinued treatment due to adverse reactions in each treatment arm.

**Table 5: Adverse Reactions (All Intensity) Reported in ≥5% of Treatment-Naïve or PegIFN/RBV-Experienced Subjects with Stage 4 or 5 Chronic Kidney Disease and HCV Treated with ZEPATIER for 12 Weeks in C-SURFER**

|          | <b>ZEPATIER<br/>N=122<br/>%<br/>12 weeks</b> | <b>Placebo<br/>N=113<br/>%<br/>12 weeks</b> |
|----------|--|---|
| Nausea   | 11%  | 8%  |
| Headache | 11%  | 5%  |
| Fatigue  | 5%   | 8%  |

Laboratory Abnormalities in Subjects Receiving ZEPATIER with or without Ribavirin

*Serum ALT Elevations*

During clinical trials with ZEPATIER with or without ribavirin, regardless of treatment duration, 1% (12/1599) of subjects experienced elevations of ALT from normal levels to greater than 5 times the ULN, generally at or after treatment week 8 (mean onset time 10 weeks, range 6-12 weeks). These late ALT elevations were typically asymptomatic. Most late ALT elevations resolved with ongoing therapy with ZEPATIER or after completion of therapy [see *Warnings and Precautions (5.2)*]. The frequency of late ALT elevations was higher in subjects with higher grazoprevir plasma concentrations [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*]. The incidence of late ALT elevations was not affected by treatment duration. Cirrhosis was not a risk factor for late ALT elevations.

*Serum Bilirubin Elevations*

During clinical trials with ZEPATIER with or without ribavirin, regardless of treatment duration, elevations in bilirubin at greater than 2.5 times ULN were observed in 6% of subjects receiving ZEPATIER with ribavirin compared to less than 1% in those receiving ZEPATIER alone. These bilirubin increases were predominately indirect and generally observed in association with ribavirin co-administration. Bilirubin elevations were typically not associated with serum ALT elevations.

*Decreased Hemoglobin*

During clinical trials with ZEPATIER with or without ribavirin, the mean change from baseline in hemoglobin levels in subjects treated with ZEPATIER for 12 weeks was -0.3 g per dL and with ZEPATIER with ribavirin for 16 weeks was approximately -2.2 g per dL. Hemoglobin declined during the first 8 weeks of treatment, remained low during the remainder of treatment, and normalized to baseline levels during follow-up. Less than 1% of subjects treated with ZEPATIER with ribavirin had hemoglobin levels decrease to less than 8.5 g per dL during treatment. No subjects treated with ZEPATIER alone had a hemoglobin level less than 8.5 g per dL.

Clinical Trial in Pediatric Subjects

Adverse Reactions in Pediatric Subjects 12 Years of Age and Older

The safety of ZEPATIER was assessed in pediatric subjects 12 years of age and older based on data from 22 subjects, without cirrhosis, who were treated with ZEPATIER for 12 weeks in a Phase 2b, open-label clinical trial (MK-5172-079). The adverse reactions observed were consistent with those observed in clinical trials of ZEPATIER in adults [see *Clinical Studies (14.6)*]. The adverse drug reactions observed in greater than or equal to 5% of subjects receiving ZEPATIER were headache (14%) and nausea (9%).

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ZEPATIER. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### Skin and Subcutaneous Tissue Disorders

Angioedema

### Hepatobiliary Disorders

Hepatic decompensation, hepatic failure [see *Warnings and Precautions (5.3)*]

## 7 DRUG INTERACTIONS

### 7.1 Potential for Drug Interactions

Grazoprevir is a substrate of OATP1B1/3 transporters. Co-administration of ZEPATIER with OATP1B1/3 inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations is contraindicated [see *Contraindications (4)*, *Clinical Pharmacology (12.3)*], and *Table 2*.

Elbasvir and grazoprevir are substrates of CYP3A and P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir appears to be minimal. Co-administration of moderate or strong inducers of CYP3A with ZEPATIER may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration of ZEPATIER with strong CYP3A inducers or efavirenz is contraindicated [see *Contraindications (4)*, *Clinical Pharmacology (12.3)*], and *Table 2*. Co-administration of ZEPATIER with moderate CYP3A inducers is not recommended [see *Warnings and Precautions (5.5)*, *Clinical Pharmacology (12.3)*], and *Table 6*. Co-administration of ZEPATIER with strong CYP3A inhibitors may increase elbasvir and grazoprevir concentrations. Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended [see *Warnings and Precautions (5.5)*, *Clinical Pharmacology (12.3)*], and *Table 6*.

### 7.2 Established and other Potentially Significant Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with ZEPATIER, doses should be readjusted after administration of ZEPATIER is completed.

Clearance of HCV infection with direct-acting antivirals may lead to changes in hepatic function, which may impact the safe and effective use of concomitant medications. For example, altered blood glucose control resulting in serious symptomatic hypoglycemia has been reported in diabetic patients in postmarketing case reports and published epidemiological studies. Management of hypoglycemia in these cases required either discontinuation or dose modification of concomitant medications used for diabetes treatment.

Frequent monitoring of relevant laboratory parameters (e.g., International Normalized Ratio [INR] in patients taking warfarin, blood glucose levels in diabetic patients) or drug concentrations of concomitant medications such as CYP450 substrates with a narrow therapeutic index (e.g., certain immunosuppressants) is recommended to ensure safe and effective use. Dose adjustments of concomitant medications may be necessary.

Table 6 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either ZEPATIER, the components of ZEPATIER (elbasvir [EBR] and grazoprevir [GZR]) as individual agents, or are predicted drug interactions that may occur with ZEPATIER [see *Contraindications (4)*, *Warnings and Precautions (5.5)*, and *Clinical Pharmacology (12.3)*].

**Table 6: Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions\***

| Concomitant Drug Class: Drug Name | Effect on Concentration <sup>†</sup> | Clinical Comment   |
|-----------------------------------|--------------------------------------|--|
| <b>Antibiotics:</b><br>Nafcillin  | ↓ EBR<br>↓ GZR                       | Co-administration of ZEPATIER with nafcillin may lead to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended. |

|  |  |  |
|--|--|--|
| <b>Antifungals:</b><br>oral Ketoconazole <sup>‡</sup>  | ↑ EBR<br>↑ GZR                                 | Co-administration of oral ketoconazole is not recommended.   |
| <b>Endothelin Antagonists:</b><br>Bosentan   | ↓ EBR<br>↓ GZR                                 | Co-administration of ZEPATIER with bosentan may lead to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.  |
| <b>Immunosuppressants:</b><br>Tacrolimus <sup>‡</sup>  | ↑ tacrolimus                                   | Frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of co-administration is recommended. |
| <b>HIV Medications:</b>  |  |  |
| Etravirine   | ↓ EBR<br>↓ GZR                                 | Co-administration of ZEPATIER with etravirine may lead to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.  |
| Elvitegravir/ cobicistat/ emtricitabine/ tenofovir (disoproxil fumarate <sup>‡</sup> or alafenamide) | ↑ EBR<br>↑ GZR                                 | Co-administration of cobicistat-containing regimens is not recommended.  |
| <b>HMG-CoA Reductase Inhibitors<sup>§</sup>:</b>   |  |  |
| Atorvastatin <sup>‡</sup>  | ↑ atorvastatin                                 | The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER. <sup>§</sup>  |
| Rosuvastatin <sup>‡</sup>  | ↑ rosuvastatin                                 | The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with ZEPATIER. <sup>§</sup>  |
| Fluvastatin<br>Lovastatin<br>Simvastatin   | ↑ fluvastatin<br>↑ lovastatin<br>↑ simvastatin | Statin-associated adverse events such as myopathy should be closely monitored. The lowest necessary dose should be used when co-administered with ZEPATIER. <sup>§</sup>                   |
| <b>Wakefulness-Promoting Agents:</b><br>Modafinil  | ↓ EBR<br>↓ GZR                                 | Co-administration of ZEPATIER with modafinil may lead to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.   |

\*This table is not all inclusive.

↓ = decrease, ↑ = increase

<sup>‡</sup>These interactions have been studied in healthy adults.

<sup>§</sup>See *Drug Interactions (7.3)* for a list of HMG Co-A reductase inhibitors without clinically relevant interactions with ZEPATIER.

### 7.3 Drugs without Clinically Significant Interactions with ZEPATIER

The interaction between the components of ZEPATIER (elbasvir or grazoprevir) or ZEPATIER and the following drugs were evaluated in clinical studies, and no dose adjustments are needed when ZEPATIER is used with the following drugs individually: acid reducing agents (proton pump inhibitors, H2 blockers, antacids), buprenorphine/naloxone, digoxin, dolutegravir, methadone, mycophenolate mofetil, oral contraceptive pills, phosphate binders, pitavastatin, pravastatin, prednisone, raltegravir, ribavirin, rilpivirine, tenofovir disoproxil fumarate, and sofosbuvir [see *Clinical Pharmacology (12.3)*].

No clinically relevant drug-drug interaction is expected when ZEPATIER is co-administered with abacavir, emtricitabine, entecavir, and lamivudine.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

No adequate human data are available to establish whether or not ZEPATIER poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of ZEPATIER (elbasvir or grazoprevir) at exposures greater than those in humans at the recommended human dose (RHD) (see *Data*). During organogenesis in the rat and rabbit, systemic exposures (AUC) were approximately 10 and 18 times (for elbasvir) and 117 and 41 times (for grazoprevir), respectively, the exposure in humans at the RHD. In rat pre/postnatal developmental studies, maternal systemic exposures (AUC) to elbasvir and grazoprevir were approximately 10 and 78 times, respectively, the exposure in humans at the RHD.













information regarding clinical recommendations, [see *Contraindications (4), Warnings and Precautions (5), and Drug Interactions (7)*].

Elbasvir and grazoprevir are substrates of CYP3A and P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir appears to be minimal. Co-administration of moderate and strong CYP3A inducers with ZEPATIER may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration of strong CYP3A4 inhibitors with ZEPATIER may increase elbasvir and grazoprevir plasma concentrations.

Grazoprevir is a substrate of OATP1B1/3. Co-administration of ZEPATIER with drugs that inhibit OATP1B1/3 transporters may result in a clinically relevant increase in grazoprevir plasma concentrations.

Elbasvir is not a CYP3A inhibitor *in vitro* and grazoprevir is a weak CYP3A inhibitor in humans. Co-administration with grazoprevir resulted in a 34% increase in plasma exposure of midazolam and a 43% increase in plasma exposure of tacrolimus (see Tables 6 and 10). Elbasvir inhibited P-gp *in vitro*, but no clinically relevant increases in concentrations of digoxin (a P-gp substrate; see Table 10) were observed by co-administration of elbasvir. Grazoprevir is not a P-gp inhibitor *in vitro*. Elbasvir and grazoprevir are inhibitors of the drug transporter breast cancer resistance protein (BCRP) at the intestinal level in humans and may increase plasma concentrations of co-administered BCRP substrates.

Clinically significant drug interactions with ZEPATIER as an inhibitor of other CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6), UGT1A1, esterases (CES1, CES2, and CatA), organic anion transporters (OAT)1 and OAT3, and organic cation transporter (OCT)2, are not expected, and multiple-dose administration of elbasvir or grazoprevir is unlikely to induce the metabolism of drugs metabolized by CYP1A2, CYP2B6, or CYP3A based on *in vitro* data.

**Table 9: Drug Interactions: Changes in Pharmacokinetics of Elbasvir or Grazoprevir in the Presence of Co-Administered Drug**

| Co-Administered Drug                    | Regimen of Co-Administered Drug | Regimen of EBR or/and GZR         | N  | Geometric Mean Ratio [90% CI] of EBR and GZR PK with/without Co-Administered Drug (No Effect=1.00) |                                |                     |                      |
|---|---------------------------------|-----------------------------------|----|--|--------------------------------|---------------------|----------------------|
|   |                                 |                                   |    |  | AUC*                           | C <sub>max</sub>    | C <sub>24</sub>      |
| Antifungal                              |                                 |                                   |    |  |                                |                     |                      |
| Ketoconazole                            | 400 mg once daily               | EBR 50 mg single-dose             | 7  | EBR  | 1.80 (1.41, 2.29)              | 1.29 (1.00, 1.66)   | 1.89 (1.37, 2.60)    |
|   | 400 mg once daily               | GZR 100 mg single-dose            | 8  | GZR  | 3.02 (2.42, 3.76)              | 1.13 (0.77, 1.67)   | 2.01 (1.49, 2.71)    |
| Antimycobacterial                       |                                 |                                   |    |  |                                |                     |                      |
| Rifampin                                | 600 mg single-dose IV           | EBR 50 mg single-dose             | 14 | EBR  | 1.22 (1.06, 1.40)              | 1.41 (1.18, 1.68)   | 1.31 (1.12, 1.53)    |
|   | 600 mg single-dose PO           | EBR 50 mg single-dose             | 14 | EBR  | 1.17 (0.98, 1.39)              | 1.29 (1.06, 1.58)   | 1.21 (1.03, 1.43)    |
|   | 600 mg PO once daily            | GZR 200 mg once daily             | 12 | GZR  | 0.93 (0.75, 1.17)              | 1.16 (0.82, 1.65)   | 0.10 (0.07, 0.13)    |
|   | 600 mg IV single-dose           | GZR 200 mg single-dose            | 12 | GZR  | 10.21 (8.68, 12.00)            | 10.94 (8.92, 13.43) | 1.77 (1.40, 2.24)    |
|   | 600 mg PO single-dose           | GZR 200 mg once daily             | 12 | GZR  | 8.35 (7.38, 9.45) <sup>†</sup> | 6.52 (5.16, 8.24)   | 1.62 (1.32, 1.98)    |
| HCV Antiviral                           |                                 |                                   |    |  |                                |                     |                      |
| EBR                                     | 20 mg once daily                | GZR 200 mg once daily             | 10 | GZR  | 0.90 (0.63, 1.28)              | 0.87 (0.50, 1.52)   | 0.94 (0.77, 1.15)    |
| GZR                                     | 200 mg once daily               | EBR 20 mg once daily              | 10 | EBR  | 1.01 (0.83, 1.24)              | 0.93 (0.76, 1.13)   | 1.02 (0.83, 1.24)    |
| HIV Protease Inhibitor                  |                                 |                                   |    |  |                                |                     |                      |
| Atazanavir/ritonavir                    | 300 mg/100 mg once daily        | EBR 50 mg once daily              | 10 | EBR  | 4.76 (4.07, 5.56)              | 4.15 (3.46, 4.97)   | 6.45 (5.51, 7.54)    |
|   | 300 mg/100 mg once daily        | GZR 200 mg once daily             | 12 | GZR  | 10.58 (7.78, 14.39)            | 6.24 (4.42, 8.81)   | 11.64 (7.96, 17.02)  |
| Darunavir/ritonavir                     | 600 mg/100 mg twice daily       | EBR 50 mg once daily              | 10 | EBR  | 1.66 (1.35, 2.05)              | 1.67 (1.36, 2.05)   | 1.82 (1.39, 2.39)    |
|   | 600 mg/100 mg twice daily       | GZR 200 mg once daily             | 13 | GZR  | 7.50 (5.92, 9.51)              | 5.27 (4.04, 6.86)   | 8.05 (6.33, 10.24)   |
| Lopinavir/ritonavir                     | 400 mg/100 mg twice daily       | EBR 50 mg once daily              | 10 | EBR  | 3.71 (3.05, 4.53)              | 2.87 (2.29, 3.58)   | 4.58 (3.72, 5.64)    |
|   | 400 mg/100 mg twice daily       | GZR 200 mg once daily             | 13 | GZR  | 12.86 (10.25, 16.13)           | 7.31 (5.65, 9.45)   | 21.70 (12.99, 36.25) |
| Ritonavir <sup>‡</sup>                  | 100 mg twice daily              | GZR 200 mg single-dose            | 10 | GZR  | 2.03 (1.60, 2.56)              | 1.15 (0.60, 2.18)   | 1.88 (1.65, 2.14)    |
| HIV Integrase Strand Transfer Inhibitor |                                 |                                   |    |  |                                |                     |                      |
| Dolutegravir                            | 50 mg single-dose               | EBR 50 mg + GZR 200 mg once daily | 12 | EBR  | 0.98 (0.93, 1.04)              | 0.97 (0.89, 1.05)   | 0.98 (0.93, 1.03)    |
|   | 50 mg single-dose               | EBR 50 mg + GZR 200 mg once daily | 12 | GZR  | 0.81 (0.67, 0.97)              | 0.64 (0.44, 0.93)   | 0.86 (0.79, 0.93)    |
| Raltegravir                             | 400 mg single-dose              | EBR 50 mg single-dose             | 10 | EBR  | 0.81 (0.57, 1.17)              | 0.89 (0.61, 1.29)   | 0.80 (0.55, 1.16)    |
|   | 400 mg twice daily              | GZR 200 mg once daily             | 11 | GZR  | 0.89 (0.72, 1.09)              | 0.85 (0.62, 1.16)   | 0.90 (0.82, 0.99)    |

| HIV Non-Nucleoside Reverse Transcriptase Inhibitor                  |  |                                   |    |     |                      |                      |                   |
|---|--|-----------------------------------|----|-----|----------------------|----------------------|-------------------|
| Efavirenz   | 600 mg once daily                      | EBR 50 mg once daily              | 10 | EBR | 0.46 (0.36, 0.59)    | 0.55 (0.41, 0.73)    | 0.41 (0.28, 0.59) |
|   | 600 mg once daily                      | GZR 200 mg once daily             | 12 | GZR | 0.17 (0.13, 0.24)    | 0.13 (0.09, 0.19)    | 0.31 (0.25, 0.38) |
| Ralpivirine   | 25 mg once daily                       | EBR 50 mg + GZR 200 mg once daily | 19 | EBR | 1.07 (1.00, 1.15)    | 1.07 (0.99, 1.16)    | 1.04 (0.98, 1.11) |
|   | 25 mg once daily                       | EBR 50 mg + GZR 200 mg once daily | 19 | GZR | 0.98 (0.89, 1.07)    | 0.97 (0.83, 1.14)    | 1.00 (0.93, 1.07) |
| HIV Nucleotide Reverse Transcriptase Inhibitor                      |  |                                   |    |     |                      |                      |                   |
| Tenofovir disoproxil fumarate                                       | 300 mg once daily                      | EBR 50 mg once daily              | 10 | EBR | 0.93 (0.82, 1.05)    | 0.88 (0.77, 1.00)    | 0.92 (0.81, 1.05) |
|   | 300 mg once daily                      | GZR 200 mg once daily             | 12 | GZR | 0.86 (0.65, 1.12)    | 0.78 (0.51, 1.18)    | 0.89 (0.78, 1.01) |
| HIV Fixed-Dose Combination Regimen                                  |  |                                   |    |     |                      |                      |                   |
| Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate | 150 mg/150 mg/200 mg/300 mg once daily | EBR 50 mg/GZR 100 mg once daily   | 21 | EBR | 2.18 (2.02, 2.35)    | 1.91 (1.77, 2.05)    | 2.38 (2.19, 2.60) |
|   |  | EBR 50 mg/GZR 100 mg once daily   | 21 | GZR | 5.36 (4.48, 6.43)    | 4.59 (3.70, 5.69)    | 2.78 (2.48, 3.11) |
| Immunosuppressant   |  |                                   |    |     |                      |                      |                   |
| Cyclosporine  | 400 mg single-dose                     | EBR 50 mg + GZR 200 mg once daily | 14 | EBR | 1.98 (1.84, 2.13)    | 1.95 (1.84, 2.07)    | 2.21 (1.98, 2.47) |
|   | 400 mg single-dose                     | EBR 50 mg + GZR 200 mg once daily | 14 | GZR | 15.21 (12.83, 18.04) | 17.00 (12.94, 22.34) | 3.39 (2.82, 4.09) |
| Mycophenolate mofetil   | 1000 mg single-dose                    | EBR 50 mg + GZR 200 mg once daily | 14 | EBR | 1.07 (1.00, 1.14)    | 1.07 (0.98, 1.16)    | 1.05 (0.97, 1.14) |
|   | 1000 mg single-dose                    | EBR 50 mg + GZR 200 mg once daily | 14 | GZR | 0.74 (0.60, 0.92)    | 0.58 (0.42, 0.82)    | 0.97 (0.89, 1.06) |
| Prednisone  | 40 mg single-dose                      | EBR 50 mg + GZR 200 mg once daily | 14 | EBR | 1.17 (1.11, 1.24)    | 1.25 (1.16, 1.35)    | 1.04 (0.97, 1.12) |
|   | 40 mg single-dose                      | EBR 50 mg + GZR 200 mg once daily | 14 | GZR | 1.09 (0.95, 1.25)    | 1.34 (1.10, 1.62)    | 0.93 (0.87, 1.00) |
| Tacrolimus  | 2 mg single-dose                       | EBR 50 mg + GZR 200 mg once daily | 16 | EBR | 0.97 (0.90, 1.06)    | 0.99 (0.88, 1.10)    | 0.92 (0.83, 1.02) |
|   | 2 mg single-dose                       | EBR 50 mg + GZR 200 mg once daily | 16 | GZR | 1.12 (0.97, 1.30)    | 1.07 (0.83, 1.37)    | 0.94 (0.87, 1.02) |
| Opioid-Substitution Therapy   |  |                                   |    |     |                      |                      |                   |
| Buprenorphine/naloxone  | 8 mg/2 mg single-dose                  | EBR 50 mg single-dose             | 15 | EBR | 1.22 (0.98, 1.52)    | 1.13 (0.87, 1.46)    | 1.22 (0.99, 1.51) |

|                        |                                  |   |                 |     |                      |                      |                      |
|------------------------|----------------------------------|---|-----------------|-----|----------------------|----------------------|----------------------|
|                        | 8-24 mg/<br>2-6 mg once<br>daily | GZR 200 mg<br>once daily                    | 12 <sup>§</sup> | GZR | 0.86 (0.63,<br>1.18) | 0.80 (0.54,<br>1.20) | 0.97 (0.77,<br>1.22) |
| Methadone              | 20-120 mg<br>once daily          | EBR 50 mg<br>once daily                     | 10 <sup>§</sup> | EBR | 1.20 (0.94,<br>1.53) | 1.23 (0.94,<br>1.62) | 1.32 (1.03,<br>1.68) |
|                        | 20-150 mg<br>once daily          | GZR 200 mg<br>once daily                    | 12 <sup>§</sup> | GZR | 1.03 (0.76,<br>1.41) | 0.89 (0.60,<br>1.32) | 0.98 (0.79,<br>1.23) |
| Acid-Reducing Agent    |                                  |   |                 |     |                      |                      |                      |
| Famotidine             | 20 mg single-<br>dose            | EBR 50 mg/<br>GZR 100 mg<br>single-dose     | 16              | EBR | 1.05 (0.92,<br>1.18) | 1.11 (0.98,<br>1.26) | 1.03 (0.91,<br>1.17) |
|                        | 20 mg single-<br>dose            | EBR 50 mg/<br>GZR 100 mg<br>single-dose     | 16              | GZR | 1.10 (0.95,<br>1.28) | 0.89 (0.71,<br>1.11) | 1.12 (0.97,<br>1.30) |
| Pantoprazole           | 40 mg once<br>daily              | EBR 50 mg/<br>GZR 100 mg<br>single-dose     | 16              | EBR | 1.05 (0.93,<br>1.18) | 1.02 (0.92,<br>1.14) | 1.03 (0.92,<br>1.17) |
|                        | 40 mg once<br>daily              | EBR 50 mg/<br>GZR 100 mg<br>single-dose     | 16              | GZR | 1.12 (0.96,<br>1.30) | 1.10 (0.89,<br>1.37) | 1.17 (1.02,<br>1.34) |
| Phosphate Binder       |                                  |   |                 |     |                      |                      |                      |
| Calcium<br>acetate     | 2668 mg<br>single-dose           | EBR 50 mg<br>+ GZR<br>100 mg<br>single-dose | 12              | EBR | 0.92 (0.75,<br>1.14) | 0.86 (0.71,<br>1.04) | 0.87 (0.70,<br>1.09) |
|                        | 2668 mg<br>single-dose           | EBR 50 mg<br>+ GZR<br>100 mg<br>single-dose | 12              | GZR | 0.79 (0.68,<br>0.91) | 0.57 (0.40,<br>0.83) | 0.77 (0.61,<br>0.99) |
| Sevelamer<br>carbonate | 2400 mg<br>single-dose           | EBR 50 mg<br>+ GZR<br>100 mg<br>single-dose | 12              | EBR | 1.13 (0.94,<br>1.37) | 1.07 (0.88,<br>1.29) | 1.22 (1.02,<br>1.45) |
|                        | 2400 mg<br>single-dose           | EBR 50 mg<br>+ GZR<br>100 mg<br>single-dose | 12              | GZR | 0.82 (0.68,<br>0.99) | 0.53 (0.37,<br>0.76) | 0.84 (0.71,<br>0.99) |
| Statin                 |                                  |   |                 |     |                      |                      |                      |
| Atorvastatin           | 20 mg single-<br>dose            | GZR 200 mg<br>once daily                    | 9               | GZR | 1.26 (0.97,<br>1.64) | 1.26 (0.83,<br>1.90) | 1.11 (1.00,<br>1.23) |
| Pitavastatin           | 1 mg single-<br>dose             | GZR 200 mg<br>once daily                    | 9               | GZR | 0.81 (0.70,<br>0.95) | 0.72 (0.57,<br>0.92) | 0.91 (0.82,<br>1.01) |
| Pravastatin            | 40 mg single-<br>dose            | EBR 50 mg<br>+ GZR<br>200 mg once<br>daily  | 12              | EBR | 0.98 (0.93,<br>1.02) | 0.97 (0.89,<br>1.05) | 0.97 (0.92,<br>1.02) |
|                        | 40 mg single-<br>dose            | EBR 50 mg<br>+ GZR<br>200 mg once<br>daily  | 12              | GZR | 1.24 (1.00,<br>1.53) | 1.42 (1.00,<br>2.03) | 1.07 (0.99,<br>1.16) |
| Rosuvastatin           | 10 mg single-<br>dose            | EBR 50 mg<br>+ GZR<br>200 mg<br>single-dose | 11              | EBR | 1.09 (0.98,<br>1.21) | 1.11 (0.99,<br>1.26) | 0.96 (0.86,<br>1.08) |
|                        | 10 mg single-<br>dose            | GZR 200 mg<br>once daily                    | 11              | GZR | 1.16 (0.94,<br>1.44) | 1.13 (0.77,<br>1.65) | 0.93 (0.84,<br>1.03) |
|                        | 10 mg single-<br>dose            | EBR 50 mg<br>+ GZR<br>200 mg once<br>daily  | 11              | GZR | 1.01 (0.79,<br>1.28) | 0.97 (0.63,<br>1.50) | 0.95 (0.87,<br>1.04) |

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Abbreviations: EBR, elbasvir; GZR, grazoprevir; IV, intravenous; PO, oral; EBR + GZR, administration of EBR and GZR as separate pills; EBR/GZR, administration of EBR and GZR as a single fixed-dose combination tablet.

\*AUC<sub>0-inf</sub> for single-dose, AUC<sub>0-24</sub> for once daily.

†AUC<sub>0-24</sub>

‡Higher doses of ritonavir have not been tested in a drug interaction study with GZR.

§The reference (EBR or GZR alone) for the analysis consisted of subjects pooled across Phase I studies.

**Table 10: Drug Interactions: Changes in Pharmacokinetics for Co-Administered Drug in the Presence of Elbasvir, Grazoprevir, or Co-Administered Elbasvir and Grazoprevir**

| Co-Administered Drug                    | Regimen of Co-Administered Drug               | EBR or/and GZR Administration | EBR or/and GZR Regimen    | N  | Geometric Mean Ratio [90% CI] of Co-Administered Drug PK with/without EBR or/and GZR (No Effect=1.00) |                   |                       |
|---|---|-------------------------------|---------------------------|----|---|-------------------|-----------------------|
|   |   |                               |                           |    | AUC*  | C <sub>max</sub>  | C <sub>trough</sub> † |
| P-gp Substrate                          |   |                               |                           |    |   |                   |                       |
| Digoxin                                 | Digoxin 0.25 mg single-dose                   | EBR                           | 50 mg once daily          | 18 | 1.11 (1.02, 1.22)   | 1.47 (1.25, 1.73) | --                    |
| CYP3A Substrate                         |   |                               |                           |    |   |                   |                       |
| Midazolam                               | Midazolam 2 mg single-dose                    | GZR                           | 200 mg once daily         | 11 | 1.34 (1.29, 1.39)   | 1.15 (1.01, 1.31) | --                    |
| CYP2C8 Substrate                        |   |                               |                           |    |   |                   |                       |
| Montelukast                             | Montelukast 10 mg single-dose                 | GZR                           | 200 mg once daily         | 23 | 1.11 (1.01, 1.20)   | 0.92 (0.81, 1.06) | 1.39 (1.25, 1.56)     |
| HCV Antiviral                           |   |                               |                           |    |   |                   |                       |
| GS-331007                               | Sofosbuvir 400 mg single-dose                 | EBR + GZR                     | 50 mg + 200 mg once daily | 16 | 1.13 (1.05, 1.21)   | 0.87 (0.78, 0.96) | 1.53 (1.43, 1.63)     |
| Sofosbuvir                              | Sofosbuvir 400 mg single-dose                 | EBR + GZR                     | 50 mg + 200 mg once daily | 16 | 2.43 (2.12, 2.79) <sup>‡</sup>  | 2.27 (1.72, 2.99) | --                    |
| HIV Protease Inhibitor                  |   |                               |                           |    |   |                   |                       |
| Atazanavir/ritonavir                    | Atazanavir 300 mg/ritonavir 100 mg once daily | EBR                           | 50 mg once daily          | 8  | 1.07 (0.98, 1.17)   | 1.02 (0.96, 1.08) | 1.15 (1.02, 1.29)     |
|   | Atazanavir 300 mg/ritonavir 100 mg once daily | GZR                           | 200 mg once daily         | 11 | 1.43 (1.30, 1.57)   | 1.12 (1.01, 1.24) | 1.23 (1.13, 1.34)     |
| Darunavir/ritonavir                     | Darunavir 600 mg/ritonavir 100 mg twice daily | EBR                           | 50 mg once daily          | 8  | 0.95 (0.86, 1.06)   | 0.95 (0.85, 1.05) | 0.94 (0.85, 1.05)     |
|   | Darunavir 600 mg/ritonavir 100 mg twice daily | GZR                           | 200 mg once daily         | 13 | 1.11 (0.99, 1.24)   | 1.10 (0.96, 1.25) | 1.00 (0.85, 1.18)     |
| Lopinavir/ritonavir                     | Lopinavir 400 mg/ritonavir 100 mg twice daily | EBR                           | 50 mg once daily          | 9  | 1.02 (0.93, 1.13)   | 1.02 (0.92, 1.13) | 1.07 (0.97, 1.18)     |
|   | Lopinavir 400 mg/ritonavir 100 mg twice daily | GZR                           | 200 mg once daily         | 13 | 1.03 (0.96, 1.16)   | 0.97 (0.88, 1.08) | 0.97 (0.81, 1.15)     |
| HIV Integrase Strand Transfer Inhibitor |   |                               |                           |    |   |                   |                       |
| Dolutegravir                            | Dolutegravir 50 mg single-dose                | EBR + GZR                     | 50 mg + 200 mg once daily | 12 | 1.16 (1.00, 1.34)   | 1.22 (1.05, 1.40) | 1.14 (0.95, 1.36)     |

|   |  |           |                           |    |                   |                   |                                |
|---|--|-----------|---------------------------|----|-------------------|-------------------|--------------------------------|
| Raltegravir   | Raltegravir<br>400 mg single-dose                  | EBR       | 50 mg single-dose         | 10 | 1.02 (0.81, 1.27) | 1.09 (0.83, 1.44) | 0.99 (0.80, 1.22) <sup>§</sup> |
|   | Raltegravir<br>400 mg twice daily                  | GZR       | 200 mg once daily         | 11 | 1.43 (0.89, 2.30) | 1.46 (0.78, 2.73) | 1.47 (1.09, 2.00)              |
| HIV Non-Nucleoside Reverse Transcriptase Inhibitor                              |  |           |                           |    |                   |                   |                                |
| Efavirenz   | Efavirenz<br>600 mg once daily                     | EBR       | 50 mg once daily          | 7  | 0.82 (0.78, 0.86) | 0.74 (0.67, 0.82) | 0.91 (0.87, 0.96)              |
|   | Efavirenz<br>600 mg once daily                     | GZR       | 200 mg once daily         | 11 | 1.00 (0.96, 1.05) | 1.03 (0.99, 1.08) | 0.93 (0.88, 0.98)              |
| Rilpivirine   | Rilpivirine<br>25 mg once daily                    | EBR + GZR | 50 mg + 200 mg once daily | 19 | 1.13 (1.07, 1.20) | 1.07 (0.97, 1.17) | 1.16 (1.09, 1.23)              |
| HIV Nucleotide Reverse Transcriptase Inhibitor                                  |  |           |                           |    |                   |                   |                                |
| Tenofovir disoproxil fumarate   | Tenofovir disoproxil fumarate<br>300 mg once daily | EBR       | 50 mg once daily          | 10 | 1.34 (1.23, 1.47) | 1.47 (1.32, 1.63) | 1.29 (1.18, 1.41)              |
|   | Tenofovir disoproxil fumarate<br>300 mg once daily | GZR       | 200 mg once daily         | 12 | 1.18 (1.09, 1.28) | 1.14 (1.04, 1.25) | 1.24 (1.10, 1.39)              |
|   | Tenofovir disoproxil fumarate<br>300 mg once daily | EBR/GZR   | 50 mg + 100 mg once daily | 13 | 1.27 (1.20, 1.35) | 1.14 (0.95, 1.36) | 1.23 (1.09, 1.40)              |
| HIV Fixed-Dose Combination Regimen  |  |           |                           |    |                   |                   |                                |
| Elvitegravir/<br>cobicistat/<br>emtricitabine/<br>tenofovir disoproxil fumarate | Elvitegravir<br>150 mg once daily                  | EBR/GZR   | 50 mg / 100 mg once daily | 22 | 1.10 (1.00, 1.21) | 1.02 (0.93, 1.11) | 1.31 (1.11, 1.55)              |
|   | Cobicistat<br>150 mg once daily                    | EBR/GZR   | 50 mg / 100 mg once daily | 22 | 1.49 (1.42, 1.57) | 1.39 (1.29, 1.50) | --                             |
|   | Emtricitabine<br>200 mg once daily                 | EBR/GZR   | 50 mg / 100 mg once daily | 22 | 1.07 (1.03, 1.10) | 0.96 (0.90, 1.02) | 1.19 (1.13, 1.25)              |
|   | Tenofovir disoproxil fumarate<br>300 mg once daily | EBR/GZR   | 50 mg / 100 mg once daily | 22 | 1.18 (1.13, 1.24) | 1.25 (1.14, 1.37) | 1.20 (1.15, 1.26)              |
| Immunosuppressant   |  |           |                           |    |                   |                   |                                |
| Cyclosporine  | Cyclosporine<br>400 mg single-dose                 | EBR + GZR | 50 mg + 200 mg once daily | 14 | 0.96 (0.90, 1.02) | 0.90 (0.85, 0.97) | 1.00 (0.92, 1.08) <sup>§</sup> |
| Mycophenolic acid   | Mycophenolate mofetil<br>1000 mg single-dose       | EBR + GZR | 50 mg + 200 mg once daily | 14 | 0.95 (0.87, 1.03) | 0.85 (0.67, 1.07) | --                             |
| Prednisolone  | Prednisone<br>40 mg single-dose                    | EBR + GZR | 50 mg + 200 mg once daily | 14 | 1.08 (1.01, 1.16) | 1.04 (0.99, 1.09) | --                             |
| Prednisone  | Prednisone<br>40 mg single-dose                    | EBR + GZR | 50 mg + 200 mg once daily | 14 | 1.08 (1.00, 1.17) | 1.05 (1.00, 1.10) | --                             |

|                             |  |           |                           |    |                                |                   |                                |
|-----------------------------|--|-----------|---------------------------|----|--------------------------------|-------------------|--------------------------------|
| Tacrolimus                  | Tacrolimus<br>2 mg single-dose                             | EBR + GZR | 50 mg + 200 mg once daily | 16 | 1.43 (1.24, 1.64)              | 0.60 (0.52, 0.69) | 1.70 (1.49, 1.94) <sup>§</sup> |
| Oral Contraceptive          |  |           |                           |    |                                |                   |                                |
| Ethinyl<br>estradiol (EE)   | 0.03 mg EE/<br>0.15 mg LNG<br>single-dose                  | EBR       | 50 mg once daily          | 20 | 1.01 (0.97, 1.05)              | 1.10 (1.05, 1.16) | --                             |
|                             |  | GZR       | 200 mg once daily         | 20 | 1.10 (1.05, 1.14)              | 1.05 (0.98, 1.12) | --                             |
| Levonorgestrel<br>(LNG)     |  | EBR       | 50 mg once daily          | 20 | 1.14 (1.04, 1.24)              | 1.02 (0.95, 1.08) | --                             |
|                             |  | GZR       | 200 mg once daily         | 20 | 1.23 (1.15, 1.32)              | 0.93 (0.84, 1.03) | --                             |
| Opioid Substitution Therapy |  |           |                           |    |                                |                   |                                |
| Buprenorphine               | Buprenorphine<br>8 mg/Naloxone<br>2 mg single-dose         | EBR       | 50 mg once daily          | 15 | 0.98 (0.89, 1.08)              | 0.94 (0.82, 1.08) | 0.98 (0.88, 1.09)              |
|                             | Buprenorphine<br>8-24 mg/<br>Naloxone<br>2-6 mg once daily | GZR       | 200 mg once daily         | 12 | 0.98 (0.81, 1.19)              | 0.90 (0.76, 1.07) | --                             |
| R-Methadone                 | Methadone<br>20-120 mg<br>once daily                       | EBR       | 50 mg once daily          | 10 | 1.03 (0.92, 1.15)              | 1.07 (0.95, 1.20) | 1.10 (0.96, 1.26)              |
|                             | Methadone<br>20-150 mg<br>once daily                       | GZR       | 200 mg once daily         | 12 | 1.09 (1.02, 1.17)              | 1.03 (0.96, 1.11) | --                             |
| S-Methadone                 | Methadone<br>20-120 mg<br>once daily                       | EBR       | 50 mg once daily          | 10 | 1.09 (0.94, 1.26)              | 1.09 (0.95, 1.25) | 1.20 (0.98, 1.47)              |
|                             | Methadone<br>20-150 mg<br>once daily                       | GZR       | 200 mg once daily         | 12 | 1.23 (1.12, 1.35)              | 1.15 (1.07, 1.25) | --                             |
| Statin                      |  |           |                           |    |                                |                   |                                |
| Atorvastatin                | Atorvastatin<br>10 mg single-dose                          | EBR + GZR | 50 mg + 200 mg once daily | 16 | 1.94 (1.63, 2.33)              | 4.34 (3.10, 6.07) | 0.21 (0.17, 0.26)              |
| Pitavastatin                | Pitavastatin<br>1 mg single-dose                           | GZR       | 200 mg once daily         | 9  | 1.11 (0.91, 1.34)              | 1.27 (1.07, 1.52) | --                             |
| Pravastatin                 | Pravastatin<br>40 mg single-dose                           | EBR + GZR | 50 mg + 200 mg once daily | 12 | 1.33 (1.09, 1.64) <sup>¶</sup> | 1.28 (1.05, 1.55) | --                             |
| Rosuvastatin                | Rosuvastatin<br>10 mg single-dose                          | EBR + GZR | 50 mg + 200 mg once daily | 12 | 2.26 (1.89, 2.69) <sup>#</sup> | 5.49 (4.29, 7.04) | 0.98 (0.84, 1.13)              |

Abbreviations: EBR, elbasvir; GZR, grazoprevir; EBR + GZR, administration of EBR and GZR as separate tablets; EBR/GZR, administration of EBR and GZR as a single fixed-dose combination tablet

\*AUC<sub>0-inf</sub> for single-dose administration; AUC<sub>0-24</sub> for once daily administration; AUC<sub>0-12</sub> for twice daily administration

<sup>†</sup>C24 for once daily administration; C12 for twice daily administration.

<sup>‡</sup>N=14

<sup>§</sup>C12

<sup>¶</sup>N=10

<sup>#</sup>N=8

## 12.4 Microbiology

### Mechanism of Action

ZEPATIER combines two direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, grazoprevir inhibited the proteolytic activity of the recombinant HCV genotype 1a, 1b, and 4a NS3/4A protease enzymes with IC<sub>50</sub> values of 7 pM, 4 pM, and 62 pM, respectively.

### Antiviral Activity

In HCV replicon assays, the EC<sub>50</sub> values of elbasvir against full-length replicons from genotypes 1a, 1b, and 4, were 4 pM, 3 pM, and 0.3 pM, respectively. The median EC<sub>50</sub> values of elbasvir against chimeric replicons encoding NS5A sequences from clinical isolates were 5 pM for genotype 1a (range 3-9 pM; N=5), 9 pM for genotype 1b (range 5-10 pM; N=4), 0.2 pM for genotype 4a (range 0.2-0.2 pM; N=2), 3,600 pM for genotype 4b (range 17 pM-34,000 pM; N=3), 0.45 pM for genotype 4d (range 0.4-0.5 pM; N=2), 1.9 pM for genotype 4f (N=1), 36.3 pM for genotype 4g (range 0.6-72 pM; N=2), 0.6 pM for genotype 4m (range 0.4-0.7 pM; N=2), 2.2 pM for genotype 4o (N=1), and 0.5 pM for genotype 4q (N=1).

In HCV replicon assays, the EC<sub>50</sub> values of grazoprevir against full-length replicons from genotypes 1a, 1b, and 4, were 0.4 nM, 0.5 nM, and 0.3 nM, respectively. The median EC<sub>50</sub> values of grazoprevir against chimeric replicons encoding NS3/4A sequences from clinical isolates were 0.8 nM for genotype 1a (range 0.4-5.1 nM; N=10), 0.3 nM for genotype 1b (range 0.2-5.9 nM; N=9), 0.3 nM for genotype 4a (N=1), 0.16 nM for genotype 4b (range 0.11-0.2 nM; N=2), and 0.24 nM for genotype 4g (range 0.15-0.33 nM; N=2).

### Combination Antiviral Activity

Evaluation of elbasvir in combination with grazoprevir or ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells. Evaluation of grazoprevir in combination with ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

### Resistance

#### In Cell Culture

HCV replicons with reduced susceptibility to elbasvir and grazoprevir have been selected in cell culture for genotypes 1a, 1b, and 4 which resulted in the emergence of resistance-associated amino acid substitutions in NS5A or NS3, respectively. The majority of amino acid substitutions in NS5A or NS3 selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterized in genotype 1a, 1b, or 4 replicons.

For elbasvir, in HCV genotype 1a replicons, single NS5A substitutions M28A/G/T, Q30D/E/H/K/R, L31M/V, H58D, and Y93C/H/N reduced elbasvir antiviral activity by 1.5- to 2,000-fold. In genotype 1b replicons, single NS5A substitutions L28M, L31F, and Y93H reduced elbasvir antiviral activity by 2- to 17-fold. In genotype 4 replicons, single NS5A substitutions L30S, M31V, and Y93H reduced elbasvir antiviral activity by 3- to 23-fold. In general, in HCV genotype 1a, 1b, or 4 replicons, combinations of elbasvir resistance-associated substitutions further reduced elbasvir antiviral activity.

For grazoprevir, in HCV genotype 1a replicons, single NS3 substitutions Y56H, R155K, A156G/T/V, and D168A/E/G/N/S/V/Y reduced grazoprevir antiviral activity by 2- to 81-fold; V36L/M, Q80K/R, or V107I single substitutions had no impact on grazoprevir antiviral activity in cell culture. In genotype 1b replicons, single NS3 substitutions F43S, Y56F, V107I, A156S/T/V, and D168A/G/V reduced grazoprevir antiviral activity by 1.5- to 375-fold. In genotype 4 replicons, single NS3 substitutions D168A/V reduced grazoprevir antiviral activity by 110- to 320-fold. In general, in HCV genotype 1a, 1b, or 4 replicons, combinations of grazoprevir resistance-associated substitutions further reduced grazoprevir antiviral activity.

### *In Clinical Studies*

In a pooled analysis of subjects treated with regimens containing ZEPATIER or elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical trials, resistance analyses of both drug targets were conducted for 50 subjects who experienced virologic failure and had sequence data available (6 with on-treatment virologic failure, 44 with post-treatment relapse). Treatment-emergent substitutions observed in the viral populations of these subjects based on HCV genotypes and subtypes are shown in Table 11. Treatment-emergent NS5A substitutions were detected in 30/37 (81%) genotype 1a-, 7/8 (88%) genotype 1b-, and 5/5 (100%) genotype 4-infected subjects. The most common treatment-emergent NS5A substitutions in genotype 1a were at position Q30 (n=22). Treatment-emergent NS3 substitutions were detected in 29/37 (78%) genotype 1a-, 2/8 (25%) genotype 1b-, and 2/5 (40%) genotype 4-infected subjects. The most common treatment-emergent NS3 substitutions in genotype 1a were at position D168 (n=18). Treatment-emergent substitutions were detected in both HCV drug targets in 23/37 (62%) genotype 1a-, 1/8 (13%) genotype 1b-, and 2/5 (40%) genotype 4-infected subjects.

**Table 11: Treatment-Emergent Amino Acid Substitutions Among Virologic Failures in the Pooled Analysis of ZEPATIER with and without Ribavirin Regimens in Phase 2 and Phase 3 Clinical Trials**

| Target | Genotype 1a<br>N = 37   | Genotype 1b<br>N = 8 | Genotype 4<br>N = 5           |
|--------|---|----------------------|-------------------------------|
| NS5A   | M28A/G/T,<br>Q30H/K/R/Y,<br>L31F/M/V, H58D,<br>Y93H/N/S             | L28M, L31F/V, Y93H   | L28S/T, M31I/V, P58D,<br>Y93H |
| NS3    | V36L/M, Y56H, V107I,<br>R155I/K, A156G/T/V,<br>V158A, D168A/G/N/V/Y | Y56F, V107I, A156T   | A156M/T/V, D168A/G,<br>V170I  |

### Persistence of Resistance-Associated Substitutions

The persistence of elbasvir and grazoprevir treatment-emergent amino acid substitutions in NS5A, and NS3, respectively, was assessed in HCV genotype 1-infected subjects in Phase 2 and 3 trials whose virus had treatment-emergent resistance-associated substitutions in the drug target, and with available data through at least 24 weeks post-treatment using population nucleotide sequence analysis.

Viral populations with treatment-emergent NS5A resistance-associated substitutions were generally more persistent than those with NS3 resistance-associated substitutions. Among genotype 1a-infected subjects, NS5A resistance-associated substitutions persisted at detectable levels at follow-up week 12 in 95% (35/37) of subjects and in 100% (9/9) of subjects with follow-up week 24 data. Among genotype 1b-infected subjects, NS5A resistance-associated substitutions persisted at detectable levels in 100% (7/7) of subjects at follow-up week 12 and in 100% (3/3) of subjects with follow-up week 24 data.

Among genotype 1a-infected subjects, NS3 resistance-associated substitutions persisted at detectable levels at follow-up week 24 in 31% (4/13) of subjects. Among genotype 1b-infected subjects, NS3 resistance-associated substitutions persisted at detectable levels at follow-up week 24 in 50% (1/2) of subjects.

Due to the limited number of genotype 4-infected subjects with treatment-emergent NS5A and NS3 resistance-associated substitutions, trends in persistence of treatment-emergent substitutions in this genotype could not be established.

The lack of detection of a virus containing a resistance-associated substitution does not necessarily indicate that viral populations carrying that substitution have declined to a background level that may have existed prior to treatment. The long-term clinical impact of the emergence or persistence of virus containing ZEPATIER-resistance-associated substitutions is unknown.

### Effect of Baseline HCV Amino Acid Polymorphisms on Treatment Response in Genotype 1-Infected Subjects

Analyses using population nucleotide sequencing were conducted to explore the association between NS5A or NS3 amino acid polymorphisms and treatment response among treatment-naïve and treatment-experienced genotype 1-infected subjects. Baseline NS5A polymorphisms at resistance-associated positions (focusing on any change from subtype reference at NS5A amino acid positions 28, 30, 31, or 93)

were evaluated. Baseline NS3 polymorphisms at positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175 were evaluated. Analyses of SVR12 rates pooled data from subjects naïve to direct-acting antivirals and who received ZEPATIER with or without ribavirin in Phase 3 clinical trials, and censored subjects who did not achieve SVR12 for reasons unrelated to virologic failure.

### *Genotype 1a*

#### *In Clinical Studies*

In genotype 1a-infected subjects, the presence of one or more HCV NS5A amino acid polymorphisms at position M28, Q30, L31, or Y93 was associated with reduced efficacy of ZEPATIER for 12 weeks (Table 12), regardless of prior treatment history or cirrhosis status. The prevalence of polymorphisms at any of these positions in genotype 1a-infected subjects was 11% (62/561) overall, and 12% (37/309) specifically for subjects in the U.S. across Phase 2 and Phase 3 clinical trials evaluating ZEPATIER for 12 weeks or ZEPATIER plus ribavirin for 16 weeks. The prevalence of polymorphisms at these positions in genotype 1a-infected subjects was 6% (35/561) at position M28, 2% (11/561) at position Q30, 3% (15/561) at position L31, and 2% (10/561) at position Y93. Polymorphisms at NS5A position H58 were common (10%) and were not associated with reduced ZEPATIER efficacy, except for a single virologic failure subject whose virus had baseline M28V and H58D polymorphisms.

The SVR12 rates for subjects treated with ZEPATIER for 12 weeks were 88% (29/33) for subjects with M28V/T/L polymorphisms (n=29, 3, and 1, respectively), 40% (4/10) for subjects with Q30H/R/L polymorphisms (n=5, 3, and 2, respectively), 38% (5/13) for subjects with an L31M polymorphism, and 63% (5/8) for subjects with Y93C/H/N/S polymorphisms (n=3, 3, 1, and 1, respectively). Although clinical trial data are limited, among genotype 1a-infected subjects with these NS5A polymorphisms who received ZEPATIER plus ribavirin for 16 weeks, six out of six subjects achieved SVR12. The specific NS5A polymorphisms observed in subjects treated with ZEPATIER plus ribavirin for 16 weeks included M28V (n=2), Q30H (n=1), L31M (n=2), or Y93C/H (n=1 each).

**Table 12: Clinical Trial Data: SVR12 in HCV Genotype 1a-Infected Subjects without or with Baseline NS5A Polymorphisms**

| <b>NS5A Polymorphism Status</b>                             | <b>ZEPATIER 12 Weeks SVR12 % (n/N)</b> | <b>ZEPATIER + RBV 16 Weeks SVR12 % (n/N)</b> |
|---|--|--|
| Without baseline NS5A polymorphism (M28, Q30, L31, or Y93)  | 98% (441/450)                          | 100% (49/49)                                 |
| With baseline NS5A polymorphism (M28*, Q30*, L31*, or Y93*) | 70% (39/56)                            | 100% (6/6)                                   |

\*Any change from GT1a reference.

There are insufficient clinical trial data to determine the impact of HCV NS5A amino acid polymorphisms in treatment-experienced subjects who failed prior PegIFN + RBV + HCV protease inhibitor therapy and received ZEPATIER with ribavirin.

In genotype 1a-infected subjects, the NS3 Q80K polymorphism did not impact treatment response. Polymorphisms at other NS3 resistance-associated positions were uncommon and were not associated with reduced treatment efficacy.

*In Postmarketing Observational Studies*

Effectiveness (SVR12 rates) in observational studies can be subject to certain biases and confounding factors that cannot be accounted for in the analyses, in part due to the nature of the study designs and populations under study.

Protocol 095

In Protocol 095, a sub-study of a prospective, observational comparative study, effectiveness of treatment with ZEPATIER plus ribavirin for 16 weeks was assessed in 29 HCV genotype 1a-infected patients with 1 or more baseline NS5A polymorphisms at amino acid positions M28, Q30, L31, and/or Y93. Overall, the SVR12 rate for patients with 1 or more baseline NS5A polymorphisms at any of the 4 amino acid positions was 93% (27/29). 23 patients had a NS5A polymorphism at a single amino acid position at baseline. The SVR12 rates for patients with a single polymorphism at amino acid position M28, Q30, L31, or Y93 were 100% (14/14), 100% (1/1), 33% (1/3), and 100% (5/5), respectively. Six patients had NS5A polymorphisms at more than 1 amino acid position (M28, Q30, L31, and/or Y93) at baseline. The SVR12 rate for these patients was 100% (6/6).

VA NS5A Cohort Study

In a retrospective Veterans Administration (VA) NS5A cohort study, effectiveness of treatment with ZEPATIER plus ribavirin for 16 weeks was assessed in 93 HCV genotype 1a-infected patients with 1 or more baseline NS5A polymorphisms at amino acid positions M28, Q30, L31, and/or Y93. Overall, the SVR12 rate for patients with 1 or more baseline NS5A polymorphisms at any of the 4 amino acid positions was 81% (75/93). 65 patients had a NS5A polymorphism at a single amino acid position at baseline. The SVR12 rates for patients with a single polymorphism at amino acid position M28, Q30, L31, or Y93 were 94% (16/17), 100% (8/8), 84% (16/19), and 81% (17/21), respectively. 28 patients had NS5A polymorphisms at more than 1 amino acid position (M28, Q30, L31, and/or Y93) at baseline. The SVR12 rate for these patients was 64% (18/28).

*Genotype 1b*

*In Clinical Studies*

In genotype 1b-infected subjects treated with ZEPATIER for 12 weeks, SVR12 rates (non-virologic failure-censored) were 94% (48/51) and 99% (247/248) for those with and without one or more NS5A polymorphisms at position 28, 30, 31, or 93.

In genotype 1b-infected subjects, baseline NS3 polymorphisms did not impact treatment response.

Effect of Baseline HCV Polymorphisms on Treatment Response in Genotype 4-Infected Subjects

Phylogenetic analysis of HCV sequences from genotype 4-infected subjects (n=71) in the pooled analyses of subjects (non-virologic failure-censored) treated with regimens containing ZEPATIER or

elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical trials identified 4 HCV genotype 4 subtypes (4a, 4d, 4k, 4o). Most subjects were infected with either subtype 4a (42%) or 4d (51%); 1 to 2 subjects were infected with each of the other genotype 4 subtypes. Among subjects enrolled at U.S. study sites, 11/13 (85%) were infected with HCV subtype 4a. There were two subjects infected with HCV subtype 4d who experienced virologic failure with the regimen containing grazoprevir and elbasvir.

In genotype 4-infected subjects, SVR12 rates for subjects with baseline NS5A polymorphisms (any change from reference at NS5A amino acid positions 28, 30, 31, 58, and 93 by population nucleotide sequencing) were 100% (28/28) and for subjects without baseline NS5A polymorphisms were 95% (41/43).

In genotype 4-infected subjects, SVR12 rates for subjects with baseline NS3 polymorphisms (any change from reference at NS3 amino acid positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175 by population nucleotide sequencing) were 100% (18/18) and for subjects without baseline NS3 polymorphisms were 96% (51/53).

#### Cross Resistance

Cross resistance is possible among NS5A inhibitors and NS3/4A protease inhibitors by class. Elbasvir and grazoprevir are fully active against viral populations with substitutions conferring resistance to NS5B inhibitors.

In the C-SALVAGE trial, subjects with genotype 1 infection who had failed prior treatment with boceprevir (n=28), simeprevir (n=8), or telaprevir (n=43) in combination with PegIFN + RBV received EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. There are limited data to determine the impact of HCV NS3 resistance-associated substitutions detected at baseline in treatment-experienced subjects who failed prior PegIFN + RBV + HCV protease inhibitor therapy and received ZEPATIER with ribavirin. SVR was achieved in 88% (21/24) of genotype 1a and genotype 1b infected subjects with NS3 resistance-associated substitutions detected at baseline. Specific NS3 substitutions observed at baseline included one or more of the following: V36L/M (n=8), T54S (n=4), S122G/T (n=9), R155K/T (n=9), A156S/T (n=1), and D168E/N (n=3). SVR was 100% (55/55) in subjects without baseline NS3 resistance substitutions. The 3 virologic failure subjects had the following NS3 or NS5A substitutions/polymorphisms at baseline: NS3 R155T/D168N, NS3 R155K plus NS5A H58D, and NS3 T54S plus NS5A L31M.

The efficacy of ZEPATIER has not been established in patients who have previously failed treatment with other regimens that included an NS5A inhibitor.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis and Mutagenesis

Elbasvir and grazoprevir were not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis, chromosomal aberration in Chinese Hamster Ovary cells, and in *in vivo* rat micronucleus assays.

Carcinogenicity studies with elbasvir or grazoprevir have not been conducted.

If ZEPATIER is administered in a regimen containing ribavirin, the information for ribavirin on carcinogenesis and mutagenesis also applies to this combination regimen. Refer to the ribavirin prescribing information for information on carcinogenesis and mutagenesis.

#### Impairment of Fertility

No effects on mating, female or male fertility, or early embryonic development were observed in rats at up to the highest dose tested. Systemic exposures (AUC) to elbasvir and grazoprevir were approximately 8 and 114 times, respectively, the exposure in humans at the recommended human dose.

If ZEPATIER is administered with ribavirin, the information for ribavirin on impairment of fertility also applies to this combination regimen. Refer to the ribavirin prescribing information for information on impairment of fertility.

## **14 CLINICAL STUDIES**

### **14.1 Overview of Clinical Trials**

The efficacy of ZEPATIER was assessed in 2 placebo-controlled trials and 4 uncontrolled Phase 2 and 3 clinical trials in 1401 subjects with genotype (GT) 1, 4, or 6 and in 1 clinical trial in 22 pediatric subjects with GT 1 or 4 chronic hepatitis C virus infection with compensated liver disease (with or without cirrhosis).

An overview of the 6 trials (n=1373) contributing to the assessment of efficacy in genotype 1 or 4 is provided in Table 13. C-EDGE TN, C-EDGE COINFECTION, C-SCAPE, and C-EDGE TE also included subjects with genotype 6 HCV infection (n=28). Because ZEPATIER is not indicated for genotype 6 infection, results in patients with genotype 6 infection are not included in Clinical Studies (14).

**Table 13: Trials Conducted with ZEPATIER**

| <b>Trial</b>                          | <b>Population</b>  | <b>Study Groups and Duration<br/>(Number of Subjects Treated)</b>  |
|---------------------------------------|--|--|
| C-EDGE TN<br>(double-blind)           | GT 1, 4<br>TN with or without cirrhosis  | <ul style="list-style-type: none"> <li>• ZEPATIER for 12 weeks (N=306)</li> <li>• Placebo for 12 weeks (N=102)</li> </ul>  |
| C-EDGE<br>COINFECTION<br>(open-label) | GT 1, 4<br>TN with or without cirrhosis<br>HCV/HIV-1 co-infection                                  | <ul style="list-style-type: none"> <li>• ZEPATIER for 12 weeks (N=217)</li> </ul>  |
| C-SURFER<br>(double-blind)            | GT 1<br>TN or TE with or without<br>cirrhosis<br>Severe Renal Impairment<br>including Hemodialysis | <ul style="list-style-type: none"> <li>• EBR* + GZR* for 12 weeks (N=122)</li> <li>• Placebo for 12 weeks (N=113)</li> </ul>   |
| C-SCAPE<br>(open-label)               | GT 4<br>TN without cirrhosis   | <ul style="list-style-type: none"> <li>• EBR* + GZR* for 12 weeks (N=10)</li> <li>• EBR* + GZR* + RBV for 12 weeks (N=10)</li> </ul>   |
| C-EDGE TE<br>(open-label)             | GT 1, 4<br>TE with or without cirrhosis<br>with or without<br>HCV/HIV-1 co-infection               | <ul style="list-style-type: none"> <li>• ZEPATIER for 12 or 16 weeks (N=105 and 101, respectively)</li> <li>• ZEPATIER + RBV for 12 or 16 weeks (N=104 and 104, respectively)</li> </ul> |
| C-SALVAGE<br>(open-label)             | GT 1<br>TE with HCV protease<br>inhibitor regimen† with or<br>without cirrhosis                    | <ul style="list-style-type: none"> <li>• EBR* + GZR* + RBV for 12 weeks (N=79)</li> </ul>  |
| MK-5172-079<br>(open-label)           | GT 1, 4<br>TN or TE pediatric subjects   | <ul style="list-style-type: none"> <li>• ZEPATIER for 12 weeks (N=22; 12 years to less than 18 years)</li> </ul>   |

GT = Genotype

TN = Treatment-Naïve

TE = Treatment-Experienced (failed prior treatment with interferon [IFN] or peginterferon alfa [PegIFN] with or without ribavirin [RBV] or were intolerant to prior therapy).

\*EBR = elbasvir 50 mg; GZR = grazoprevir 100 mg; EBR + GZR = co-administered as single agents.

† Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with PegIFN + RBV.

ZEPATIER was administered once daily by mouth in these trials. For subjects who received ribavirin (RBV), the RBV dosage was weight-based (less than 66 kg = 800 mg per day, 66 to 80 kg = 1000 mg per day, 81 to 105 kg = 1200 mg per day, greater than 105 kg = 1400 mg per day) administered by mouth in two divided doses with food.

Sustained virologic response (SVR) was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR12). Serum HCV RNA values were measured during these clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with an LLOQ of 15 HCV RNA IU per mL, with the exception of C-SCAPE where the assay had an LLOQ of 25 HCV RNA IU per mL.

#### **14.2 Clinical Trials in Treatment-Naïve Subjects with Genotype 1 HCV (C-EDGE TN and C-EDGE COINFECTION)**

The efficacy of ZEPATIER in treatment-naïve subjects with genotype 1 chronic hepatitis C virus infection with or without cirrhosis was demonstrated in the C-EDGE TN and C-EDGE COINFECTION trials.

C-EDGE TN was a randomized, double-blind, placebo-controlled trial in treatment-naïve subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects were randomized in a 3:1 ratio to ZEPATIER for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with ZEPATIER for 12 weeks (deferred treatment group). Among subjects with genotype 1 infection randomized to the immediate treatment group, the median age was 55 years (range: 20 to 78); 56% of the subjects were male; 61% were White; 20% were Black or African American; 8% were Hispanic or Latino; mean body mass index was 26 kg/m<sup>2</sup>; 72% had baseline HCV RNA levels greater than 800,000 IU per mL; 24% had cirrhosis; 67% had non-C/C IL28B alleles (CT or TT); and 55% had genotype 1a and 45% had genotype 1b chronic HCV infection.

C-EDGE COINFECTION was an open-label, single-arm trial in treatment-naïve HCV/HIV-1 co-infected subjects with genotype 1 or 4 infection with or without cirrhosis. Subjects received ZEPATIER for 12 weeks. Among subjects with genotype 1 infection, the median age was 50 years (range: 21 to 71); 85% of the subjects were male; 75% were White; 19% were Black or African American; 6% were Hispanic or Latino; mean body mass index was 25 kg/m<sup>2</sup>; 59% had baseline HCV RNA levels greater than 800,000 IU per mL; 16% had cirrhosis; 65% had non-C/C IL28B alleles (CT or TT); and 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection.

Table 14 presents treatment outcomes for ZEPATIER in treatment-naïve subjects with genotype 1 infection from C-EDGE TN (immediate treatment group) and C-EDGE COINFECTION. For treatment outcomes for ZEPATIER in genotype 4 infection, [see *Clinical Studies (14.5)*].

**Table 14: C-EDGE TN and C-EDGE COINFECTION: SVR12 in Treatment-Naïve Subjects with or without Cirrhosis with Genotype 1 HCV Treated with ZEPATIER for 12 Weeks**

| Trial                            | C-EDGE TN<br>(Immediate Treatment<br>Group) | C-EDGE<br>COINFECTION<br>(HCV/HIV-1<br>Co-Infection) |
|----------------------------------|---|--|
| Regimen                          | ZEPATIER<br>12 Weeks<br>N=288               | ZEPATIER<br>12 Weeks<br>N=189                        |
| SVR in Genotype 1                | 95% (273/288)                               | 95% (179/189)  |
| Outcome for subjects without SVR |   |  |
| On-treatment Virologic Failure*  | <1% (1/288)                                 | 0% (0/189)   |
| Relapse                          | 3% (10/288)                                 | 3% (6/189)   |
| Other†                           | 1% (4/288)                                  | 2% (4/189)   |
| SVR by Genotype 1 Subtypes       |   |  |
| GT 1a‡                           | 92% (144/157)                               | 94% (136/144)  |
| GT 1b§                           | 98% (129/131)                               | 96% (43/45)  |
| SVR by Cirrhosis status          |   |  |
| Non-cirrhotic                    | 94% (207/220)                               | 94% (148/158)  |
| Cirrhotic                        | 97% (66/68)                                 | 100% (31/31)   |

\*Includes subjects with virologic breakthrough.

†Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

‡For the impact of baseline NS5A polymorphisms on SVR12, [see *Microbiology (12.4)*], Table 12.

§Includes genotype 1 subtypes other than 1a or 1b.

### 14.3 Clinical Trials in Treatment-Experienced Subjects with Genotype 1 HCV

#### Treatment-Experienced Subjects who Failed Prior PegIFN with RBV Therapy (C-EDGE TE)

C-EDGE TE was a randomized, open-label comparative trial in subjects with genotype 1 or 4 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior therapy with PegIFN + RBV therapy. Subjects were randomized in a 1:1:1:1 ratio to one of the following treatment groups: ZEPATIER for 12 weeks, ZEPATIER + RBV for 12 weeks, ZEPATIER for 16 weeks, or ZEPATIER

+ RBV for 16 weeks. Among subjects with genotype 1 infection, the median age was 57 years (range: 19 to 77); 64% of the subjects were male; 67% were White; 18% were Black or African American; 9% were Hispanic or Latino; mean body mass index was 28 kg/m<sup>2</sup>; 78% had baseline HCV RNA levels greater than 800,000 IU/mL; 34% had cirrhosis; 79% had non-C/C IL28B alleles (CT or TT); and 60% had genotype 1a, 39% had genotype 1b, and 1% had genotype 1-Other chronic HCV infection.

Treatment outcomes in genotype 1 subjects treated with ZEPATIER for 12 weeks or ZEPATIER with RBV for 16 weeks are presented in Table 15. Treatment outcomes with ZEPATIER with RBV for 12 weeks or without RBV for 16 weeks are not shown because these regimens are not recommended in PegIFN/RBV-experienced genotype 1 patients. For treatment outcomes for ZEPATIER in genotype 4 infection, [see *Clinical Studies (14.5)*].

**Table 15: C-EDGE TE: SVR12 in Treatment-Experienced Subjects who Failed Prior PegIFN with RBV with or without Cirrhosis, with or without HCV/HIV-1 Co-infection with Genotype 1 HCV Treated with ZEPATIER for 12 Weeks or ZEPATIER with Ribavirin for 16 Weeks**

| Regimen                              | ZEPATIER<br>12 weeks<br>N=96 | ZEPATIER + RBV<br>16 weeks<br>N=96 |
|--------------------------------------|------------------------------|------------------------------------|
| SVR in Genotype 1                    | 94% (90/96)                  | 97% (93/96)                        |
| Outcome for subjects without SVR     |                              |                                    |
| On-treatment Virologic Failure*      | 0% (0/96)                    | 0% (0/96)                          |
| Relapse                              | 5% (5/96)                    | 0% (0/96)                          |
| Other†                               | 1% (1/96)                    | 3% (3/96)                          |
| SVR by Genotype 1 Subtypes           |                              |                                    |
| GT 1a‡                               | 90% (55/61)                  | 95% (55/58)                        |
| GT 1b§                               | 100% (35/35)                 | 100% (38/38)                       |
| SVR by Cirrhosis status              |                              |                                    |
| Non-cirrhotic                        | 94% (61/65)                  | 95% (61/64)                        |
| Cirrhotic                            | 94% (29/31)                  | 100% (32/32)                       |
| SVR by Response to Prior HCV Therapy |                              |                                    |
| On-treatment Virologic Failure¶      | 90% (57/63)                  | 95% (58/61)                        |
| Relapser                             | 100% (33/33)                 | 100% (35/35)                       |

\*Includes subjects with virologic breakthrough or rebound.

†Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

‡For the impact of baseline NS5A polymorphisms on SVR, [see *Microbiology (12.4)*], Table 12.

§Includes genotype 1 subtypes other than 1a or 1b.

¶Includes prior null responders and partial responders.

#### Treatment-Experienced Subjects who Failed Prior PegIFN + RBV + HCV Protease Inhibitor Therapy (C-SALVAGE)

C-SALVAGE was an open-label single-arm trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with PegIFN + RBV. Subjects received EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. Subjects had a median age of 55 years (range: 23 to 75); 58% of the subjects were male; 97% were White; 3% were Black or African American; 15% were Hispanic or Latino; mean body mass index was 28 kg/m<sup>2</sup>; 63% had baseline HCV RNA levels greater than 800,000 IU/mL; 43% had cirrhosis; and 97% had non-C/C IL28B alleles (CT or TT); 46% had baseline NS3 resistance-associated substitutions.

Overall SVR was achieved in 96% (76/79) of subjects receiving EBR + GZR + RBV for 12 weeks. Four percent (3/79) of subjects did not achieve SVR due to relapse. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were generally consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions [see *Microbiology (12.4)*].

#### **14.4 Clinical Trial in Subjects with Genotype 1 HCV and Severe Renal Impairment including Subjects on Hemodialysis (C-SURFER)**

C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic kidney disease (CKD) Stage 4 (eGFR 15-29 mL/min/1.73 m<sup>2</sup>) or CKD Stage 5 (eGFR <15 mL/min/1.73 m<sup>2</sup>), including subjects on hemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or PegIFN ± RBV therapy. Subjects were randomized in a 1:1 ratio to one of the following treatment groups: EBR 50 mg once daily + GZR 100 mg once daily for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with EBR + GZR for 12 weeks (deferred treatment group). In addition, 11 subjects received open-label EBR + GZR for 12 weeks (intensive pharmacokinetic [PK] group). Subjects randomized to the immediate treatment group and intensive PK group had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 45% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 6% had cirrhosis; and 72% had non-C/C IL28B alleles (CT or TT).

Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the pooled immediate treatment group and intensive PK group are presented in Table 16.

**Table 16: C-SURFER: SVR12 in Subjects with Severe Renal Impairment including Subjects on Hemodialysis who were Treatment-Naïve or had Failed Prior IFN or PegIFN ± RBV, with or without Cirrhosis, with Genotype 1 HCV Treated with ZEPATIER for 12 Weeks**

| Regimen                             | EBR + GZR<br>12 weeks<br>(Immediate Treatment Group)<br>N=122* |
|-------------------------------------|--|
| Overall SVR                         | 94% (115/122) <sup>†</sup>                                     |
| Outcome for subjects without SVR    |  |
| On-treatment Virologic Failure      | 0% (0/122)   |
| Relapse                             | <1% (1/122)  |
| Other <sup>‡</sup>                  | 5% (6/122)   |
| SVR by Genotype                     |  |
| GT 1a                               | 97% (61/63)  |
| GT 1b <sup>§</sup>                  | 92% (54/59)  |
| SVR by Cirrhosis status             |  |
| No                                  | 95% (109/115)  |
| Yes                                 | 86% (6/7)  |
| SVR by Prior HCV Treatment Status   |  |
| Treatment-naïve                     | 95% (96/101)   |
| Treatment-experienced               | 90% (19/21)  |
| SVR by Dialysis Status              |  |
| No                                  | 97% (29/30)  |
| Yes                                 | 93% (86/92)  |
| SVR by Chronic Kidney Disease Stage |  |
| Stage 4                             | 100% (22/22)   |
| Stage 5                             | 93% (93/100)   |

\*Includes subjects (n=11) in the intensive PK group.

<sup>†</sup>SVR was achieved in 99% (115/116) of subjects in the pre-specified primary analysis population, which excluded subjects not receiving at least one dose of study treatment and those with missing data due to death or early study discontinuation for reasons unrelated to treatment response.

<sup>‡</sup>Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

<sup>§</sup>Includes genotype 1 subtypes other than 1a or 1b.

#### 14.5 Clinical Trials with Genotype 4 HCV

The efficacy of ZEPATIER in subjects with genotype 4 chronic HCV infection was demonstrated in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SCAPE. C-SCAPE was a randomized, open-label trial which included treatment-naïve subjects with genotype 4 infection without cirrhosis. Subjects were randomized in a 1:1 ratio to EBR 50 mg once daily + GZR 100 mg once daily for 12 weeks or EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. In these combined studies in subjects with

genotype 4 infection, 64% were treatment-naïve; 66% of the subjects were male; 87% were White; 10% were Black or African American; 22% had cirrhosis; and 30% had HCV/HIV-1 co-infection.

In C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION trials combined, a total of 66 genotype 4 treatment-naïve subjects received ZEPATIER or EBR + GZR for 12 weeks. In these combined trials, SVR12 among subjects treated with ZEPATIER or EBR + GZR for 12 weeks was 97% (64/66).

In C-EDGE TE, a total of 37 genotype 4 treatment-experienced subjects received a 12- or 16-week ZEPATIER with or without RBV regimen. SVR12 among randomized subjects treated with ZEPATIER + RBV for 16 weeks was 100% (8/8).

#### **14.6 Clinical Trial in Pediatric Subjects with Genotype 1 or 4 Chronic Hepatitis C Infection**

The efficacy of ZEPATIER was evaluated in an open-label study (MK-5172-079, NCT03379506) that evaluated pediatric subjects 12 years to less than 18 years of age who received ZEPATIER for 12 weeks. HCV GT1a infected subjects with one or more baseline NS5A RAS were excluded from study participation. In the MK-5172-079 study, 22 treatment-naïve or treatment-experienced subjects 12 years to less than 18 years of age with genotype 1 (n=21) or 4 CHC (n=1), without cirrhosis, were treated with ZEPATIER for 12 weeks. The median age was 13.5 years (range: 12 to 17); 50% were female; 95% were White; the weight range was 28.1 kg to 96.5 kg; 95.5% had genotype 1 and 4.5% had genotype 4; 64% were treatment-naïve, 36% were treatment-experienced; 46% had baseline HCV RNA levels greater than 800,000 IU/mL. The overall SVR12 rate was 100% (22/22).

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Each ZEPATIER tablet contains 50 mg elbasvir and 100 mg grazoprevir, is beige, oval-shaped, film-coated, debossed with “770” on one side and plain on the other. The tablets are packaged into a carton (NDC 0006-3074-02) containing two (2) 14-count child-resistant dose packs for a total of 28 tablets.

Store ZEPATIER in the original blister package until use to protect from moisture.

Store ZEPATIER at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F) [see USP Controlled Room Temperature].

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

For patients receiving ZEPATIER with ribavirin, advise patients to read the FDA-approved patient labeling (Medication Guide) for ribavirin [see *Warnings and Precautions* (5.4)].

#### Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Inform patients that HBV reactivation can occur in patients coinfecting with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of hepatitis B virus infection [see *Warnings and Precautions* (5.1)].

#### Risk of Hepatic Decompensation/Failure in Patients with Evidence of Advanced Liver Disease

Advise patients to seek medical evaluation immediately for symptoms of worsening liver problems such as nausea, tiredness, yellowing of the skin or white part of the eyes, bleeding or bruising more easily than normal, confusion, loss of appetite, diarrhea, dark or brown urine, dark or bloody stool, swelling of the stomach area (abdomen) or pain in the upper right side of the stomach area, sleepiness, or vomiting of blood [see *Warnings and Precautions* (5.3)].

#### Risk of ALT Elevations

Inform patients to watch for early warning signs of liver inflammation, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice and discolored feces, and to

consult their healthcare professional without delay if such symptoms occur [see *Warnings and Precautions (5.2) and Adverse Reactions (6.1)*].

#### Pregnancy

Advise patients taking ZEPATIER with ribavirin to avoid pregnancy during treatment and within 6 months of stopping ribavirin and to notify their healthcare provider immediately in the event of a pregnancy [see *Use in Specific Populations (8.1)*].

#### Drug Interactions

Inform patients that ZEPATIER may interact with some drugs; therefore, advise patients to report the use of any prescription, non-prescription medication, or herbal products to their healthcare provider [see *Contraindications (4), Warnings and Precautions (5.5), and Drug Interactions (7)*].

#### Storage

Advise patients to store ZEPATIER in the original package until use to protect from moisture [see *How Supplied/Storage and Handling (16)*].

#### Administration

Advise patients to take ZEPATIER every day at the regularly scheduled time with or without food. Inform patients that it is important not to miss or skip doses and to take ZEPATIER for the duration that is recommended by the healthcare provider.

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Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of  
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

For patent information: [www.merck.com/product/patent/home.html](http://www.merck.com/product/patent/home.html)

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**Patient Information**  
**ZEPATIER® (ZEP-ah-teer)**  
(elbasvir and grazoprevir)  
tablets

**What you need to know about ZEPATIER**

- Before you take this medicine, be sure you understand what it is for and how to take it safely.
- Keep this information.
- If you have questions about this medicine, ask your healthcare provider or pharmacist.
- Every time you get a refill, look at the Patient Information. There may be new information.
- Your healthcare provider may prescribe ZEPATIER with a medicine called ribavirin. Ribavirin is also known as Rebetol®, Copegus®, Ribasphere®, and Moderiba®. **If you take ZEPATIER and ribavirin, be sure you read the Medication Guide for ribavirin.**

**What is the most important information I should know about ZEPATIER?**

---

**ZEPATIER can cause serious side effects, including,**

**Hepatitis B virus reactivation:** Before starting treatment with ZEPATIER, your healthcare provider will do blood tests to check for hepatitis B virus infection. If you have ever had hepatitis B virus infection, the hepatitis B virus could become active again during or after treatment of hepatitis C virus infection with ZEPATIER. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems including liver failure and death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop taking ZEPATIER.

**For more information about side effects, see the section “What are the possible side effects of ZEPATIER?”**

**What is ZEPATIER®?**

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ZEPATIER is a prescription medicine used with or without ribavirin to treat chronic (long-lasting) hepatitis C virus (HCV) genotypes 1 or 4 infection in adults and children 12 years of age and older or weighing at least 66 pounds (30 kilograms).

ZEPATIER should not be used in children younger than 12 years of age who weigh less than 66 pounds (30 kilograms).

It is not known if ZEPATIER is safe or effective in people awaiting a liver transplant or people who have had a liver transplant.

**Who should not take ZEPATIER?**

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Do not take ZEPATIER if you have certain liver problems.

## What should I tell my healthcare provider before taking ZEPATIER?

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**Before taking ZEPATIER, tell your healthcare provider about all of your medical conditions, including if you:**

- have ever had hepatitis B virus infection
- have liver problems other than hepatitis C
- have ever taken any medicine for hepatitis C
- have HIV
- have had or are waiting for a liver transplant
- are pregnant or trying to get pregnant. ZEPATIER has not been studied in pregnant women. We do not know if ZEPATIER will harm your baby while you are pregnant.
  - **Males and females who take ZEPATIER and ribavirin should also read the ribavirin Medication Guide for important pregnancy, contraception, and infertility information.**
- are breastfeeding or plan to breastfeed. We do not know if ZEPATIER gets in your breast milk and gets passed to your baby.
  - **Talk to your healthcare provider about the best way to feed your baby during treatment with ZEPATIER.**

## Are you taking other medicines?

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**Tell your healthcare provider about all of the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZEPATIER may affect the way other medicines work, and other medicines may affect how ZEPATIER works. Some medicines cannot be taken with ZEPATIER. Your healthcare provider can tell you if it is safe to take ZEPATIER with other medicines.

- Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.
- You can ask your healthcare provider or pharmacist for a list of medicines that interact with this medicine.
- **Do not start taking a new medicine without telling your healthcare provider.**

## How do I take ZEPATIER?

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- **Take 1 ZEPATIER tablet at the same time every day.**
- ZEPATIER comes in a blister package of individually-packaged tablets. Keep the tablets in this package until you are ready to take your dose.
- Take ZEPATIER exactly as your healthcare provider tells you to take it.
- Take ZEPATIER with or without food.
- Do not stop taking ZEPATIER without first talking with your healthcare provider.
- If you take more than your prescribed dose, call your healthcare provider right away.

## What if I forget to take ZEPATIER?

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- Do not take two doses of ZEPATIER at the same time to make up for a missed dose.
- If you are not sure what to do, call your healthcare provider or pharmacist. It is important that you do not miss or skip doses of ZEPATIER during treatment.

## What are the possible side effects of ZEPATIER?

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### **ZEPATIER can cause serious side effects, including:**

**Hepatitis B virus reactivation.** See “What is the most important information I should know about ZEPATIER?”

**Signs of liver problems. ZEPATIER may cause increases in your liver-related blood tests.** This could be a sign of serious liver problems. Your healthcare provider will do blood tests to check your liver before and during treatment with ZEPATIER. Tell your healthcare provider right away if you get any of the following symptoms or if they get worse during treatment with ZEPATIER:

- loss of appetite
- nausea and vomiting
- feeling tired or weak
- confusion
- sleepiness
- vomiting of blood
- yellowing of your skin or eyes
- color changes in your stool or urine
- bleeding or bruising more easily than normal
- diarrhea
- swelling of the stomach area (abdomen) or pain in the upper right side of the stomach area

### **Common side effects of ZEPATIER when used without ribavirin include:**

- feeling tired
- headache
- nausea
- trouble sleeping
- diarrhea

### **Common side effects of ZEPATIER when used with ribavirin include:**

- low red blood cell counts (anemia)
- headache
- feeling tired
- shortness of breath
- rash or itching
- feeling irritable
- stomach pain
- depression
- joint pain

**If you have any side effect that bothers you or that does not go away, tell your healthcare provider.**

There may be other side effects to ZEPATIER that are not listed.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information or medical advice call your doctor.

## Where should I keep ZEPATIER?

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- Keep ZEPATIER in its original packaging (blister package) until you are ready to take it. Do not take the tablets out of the original blister package to store in another container such as a pill box. This is important because the tablets are sensitive to moisture. The package is designed to protect them.
- Keep ZEPATIER at room temperature.
- Keep ZEPATIER and all medicines out of the reach of children.

## General information about ZEPATIER

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- Medicines are sometimes prescribed for purposes other than those listed in the patient information. Do not use ZEPATIER for a condition for which it was not prescribed. Do not give ZEPATIER to other people, even if they have the same condition. It may harm them.
- If you would like more information, talk with your healthcare provider or pharmacist. You can ask them for information about ZEPATIER that was written for health professionals.
- For more information, call Merck, the company that makes ZEPATIER, at 1-877-888-4231 or go to [www.ZEPATIER.com](http://www.ZEPATIER.com).

## What are the ingredients in ZEPATIER?

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The active ingredients are: elbasvir and grazoprevir.

The inactive ingredients are: colloidal silicon dioxide, copovidone, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, sodium chloride, sodium lauryl sulfate, and vitamin E polyethylene glycol succinate.

The tablets are film-coated with a coating material containing the following inactive ingredients: carnauba wax, ferrousferic oxide, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

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This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of  
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

For patent information: [www.merck.com/product/patent/home.html](http://www.merck.com/product/patent/home.html)

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Revised: 12/2021

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