CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208261Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPATIER safely and effectively. See full prescribing information for ZEPATIER.

ZEPATIER™ (elbasvir and grazoprevir) tablets, for oral use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------

ZEPATIER is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor, and is indicated with or without r bavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Testing prior to initiation:
  - Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended. (2.1)
  - Obtain hepatic laboratory testing. (2.1)
- Recommended dosage: One tablet taken orally once daily with or without food. (2.2)

Dosage Regimens and Durations for ZEPATIER in Patients with Genotype 1 or 4 HCV with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†	ZEPATIER	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†	ZEPATIER + r bavirin	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*	ZEPATIER	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI-experienced‡	ZEPATIER + r bavirin	12 weeks
Genotype 4: Treatment-naïve	ZEPATIER	12 weeks
Genotype 4: PegIFN/RBV-experienced*	ZEPATIER + r bavirin	16 weeks

*Peginterferon alfa + r bavirin.
†Polymorphisms at amino acid positions 28, 30, 31, or 93.
‡Peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor.

- HCV/HIV-1 co-infection: Follow the dosage recommendations in the table above. (2.2)
- Renal Impairment, including hemodialysis: No dosage adjustment of ZEPATIER is recommended. Refer to ribavirin prescribing information for ribavirin dosing and dosage modifications. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 50 mg e basvir and 100 mg grazoprevir (3)

----------CONTRAINDICATIONS----------

- Patients with moderate or severe hepatic impairment (Child-Pugh B or C). (4)
- OATP1B1/3 inhibitors, strong CYP3A inducers, and efavirenz. (4)
- If ZEPATIER is administered with ribavirin, the contraindications to r bavirin also apply. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- ALT elevations: Perform hepatic laboratory testing prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, perform additional hepatic laboratory testing at treatment week 12. For ALT elevations on ZEPATIER, follow recommendations in full prescribing information. (5.1)
- Risk associated with r bavirin combination treatment: If ZEPATIER is administered with r bavirin, the warnings and precautions for ribavirin also apply. (5.2)

---------- ADVERSE REACTIONS ----------

In subjects receiving ZEPATIER for 12 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% in placebo-controlled trials) were fatigue, headache, and nausea. In subjects receiving ZEPATIER with ribavirin for 16 weeks, the most commonly reported adverse reactions of moderate or severe intensity (greater than or equal to 5%) were anemia and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Co-administration of ZEPATIER with moderate CYP3A inducers is not recommended as they may decrease the plasma concentration of ZEPATIER. (7)
- Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended as they may increase the plasma concentration of ZEPATIER. (7)
- Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.3, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZEPATIER™ is indicated with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) genotypes 1 or 4 infection in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to the Initiation of Therapy

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 11*.

Hepatic Laboratory Testing

Obtain hepatic laboratory testing prior to and during treatment with ZEPATIER *[see Warnings and Precautions (5.1)].*

2.2 Recommended Dosage in Adults

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.

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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[†]	ZEPATIER	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms[†]	ZEPATIER + RBV[‡]	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*	ZEPATIER	12 weeks
Genotype 1a[§] or 1b: PegIFN/RBV/PI-experienced[¶]	ZEPATIER + RBV[‡]	12 weeks
Genotype 4: Treatment-Naïve	ZEPATIER	12 weeks
Genotype 4: PegIFN/RBV-experienced*	ZEPATIER + RBV[‡]	16 weeks

*Patients who have failed treatment with peginterferon alfa (PegIFN) + ribavirin (RBV).
[†]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.
[‡]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.
[§]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.
[¶]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) *[see Contraindications (4), 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 (5.1), Use in Specific Populations (8.9), and Clinical Pharmacology (12.3)]*.

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- ZEPATIER is contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of cytochrome P450 3A (CYP3A), and efavirenz *[see Warnings and Precautions (5.3), 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

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comment*
Anticonvulsants	Phenytoin 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[†]	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 Darunavir Lopinavir Saquinavir 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 inhibit OATP1B1/3 or strongly induce CYP3A.
[†]Efavirenz is included as a strong CYP3A inducer in this table, since co-administration reduced grazoprevir exposure by ≥80% *[see Table 8]*.

5 WARNINGS AND PRECAUTIONS

5.1 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 INR.

5.2 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)]*.

5.3 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 (5.1)].*

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.

The safety of ZEPATIER 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)]*.

<u>Adverse Reactions with ZEPATIER in Treatment-Naïve Subjects</u>

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 N=316 % 12 weeks	**Placebo N=105 % 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^3 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 N=105 % 12 weeks	**ZEPATIER + Ribavirin N=106 % 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^3 was observed at the end of 12 weeks of treatment with ZEPATIER alone. In subjects treated with ZEPATIER with ribavirin for 16 weeks,

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CD4+ T-cell counts decreased a median of 135 cells per mm^3 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

	ZEPATIER N=122 % 12 weeks	**Placebo N=113 % 12 weeks**
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 (5.1)]*. 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.

7 DRUG INTERACTIONS

7.1 Potential for Drug Interactions

Grazoprevir is a substrate of OATP1B1/3 transporters. Co-administration of ZEPATIER with drugs that inhibit OATP1B1/3 transporters may result in a significant increase in the plasma concentrations of grazoprevir. As such, co-administration of ZEPATIER with OATP1B1/3 inhibitors 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 (5.3), 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 (5.3), 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.

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 (5.3), and Clinical Pharmacology (12.3)]*.

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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[†]	Clinical Comment
Antibiotics: nafcillin	↓ EBR ↓ GZR	Co-administration of ZEPATIER with nafcillin, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.
Antifungals: ketoconazole[‡]	↑ EBR ↑ GZR	Concomitant use of systemic ketoconazole and ZEPATIER increases grazoprevir exposure and may increase the overall risk of hepatotoxicity; co-administration of ketoconazole is not recommended.
Endothelin Antagonists: bosentan	↓ EBR ↓ GZR	Co-administration of ZEPATIER with bosentan, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.
Immunosuppressants: tacrolimus[‡]	↑ tacrolimus	Co-administration of ZEPATIER with systemic tacrolimus increases the concentrations of 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.
HIV Medications:		
etravirine	↓ EBR ↓ GZR	Co-administration of ZEPATIER with etravirine, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.
elvitegravir/ cobicistat/ emtricitabine/ tenofovir (disoproxil fumarate or alafenamide)	↑ EBR ↑ GZR	Co-administration of ZEPATIER with these cobicistat-containing regimens may increase the concentrations of EBR and GZR. Co-administration is not recommended.
HMG-CoA Reductase Inhibitors[§]:		
atorvastatin[‡]	↑ atorvastatin	Co-administration of EBR and GZR with atorvastatin increases the concentrations of atorvastatin. The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER.[§]
rosuvastatin[‡]	↑ rosuvastatin	Co-administration of EBR and GZR with rosuvastatin increases the concentrations of rosuvastatin. The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with ZEPATIER.[§]
fluvastatin lovastatin simvastatin	↑ fluvastatin ↑ lovastatin ↑ simvastatin	Co-administration of ZEPATIER with these statins has not been studied but may increase the concentrations of these statins. Statin-associated adverse events such as myopathy should be closely monitored. The lowest necessary dose should be used when co-administered with ZEPATIER.[§]
Wakefulness-Promoting Agents: modafinil	↓ EBR ↓ GZR	Co-administration of ZEPATIER with modafinil, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.

*This table is not all inclusive.
[†]↓ = decrease, ↑ = increase
[‡]These interactions have been studied in healthy adults.
[§]*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 in (8.1)]*. 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.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

If ZEPATIER is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy.

Data

Animal Data

Elbasvir: Elbasvir was administered orally at up to 1000 mg/kg/day to pregnant rats and rabbits on gestation days 6 to 20 and 7 to 20, respectively, and also to rats on gestation day 6 to lactation/post-partum day 20. No effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at up to the highest dose tested. Systemic exposures (AUC) to elbasvir were approximately 10 (rats) and 18 (rabbits) times the exposure in humans at the RHD. In both species, elbasvir has been shown to cross the placenta, with fetal plasma concentrations of up to 0.8% (rabbits) and 2.2% (rats) that of maternal concentrations observed on gestation day 20.

Grazoprevir: Grazoprevir was administered to pregnant rats (oral doses up to 400 mg/kg/day) and rabbits (intravenous doses up to 100 mg/kg/day) on gestation days 6 to 20 and 7 to 20, respectively, and also to rats (oral doses up to 400 mg/kg/day) on gestation day 6 to lactation/post-partum day 20. No effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at up to the highest dose tested. Systemic exposures (AUC) to grazoprevir were ≥78 (rats) and 41 (rabbits) times the exposure in humans at the RHD. In both species, grazoprevir has been shown to cross the placenta, with fetal plasma concentrations of up to 7% (rabbits) and 89% (rats) that of maternal concentrations observed on gestation day 20.

8.2 Lactation

Risk Summary

It is not known whether ZEPATIER is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, the components of ZEPATIER (elbasvir and grazoprevir) were present in milk, without effects on growth and development observed in nursing pups *[see Data in (8.2)]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEPATIER and any potential adverse effects on the breastfed child from ZEPATIER or from the underlying maternal condition.

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If ZEPATIER is administered with ribavirin, the information for ribavirin with regard to nursing mothers also applies to this combination regimen. Refer to the ribavirin prescribing information for information on use during lactation.

Data

Elbasvir: No effects of elbasvir on growth and postnatal development were observed in nursing pups at up to the highest dose tested *[see Data in (8.1)]*. Maternal systemic exposure (AUC) to elbasvir was approximately 10 times the exposure in humans at the RHD. Elbasvir was excreted into the milk of lactating rats following oral administration (1000 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations approximately 4 times that of maternal plasma concentrations observed 2 hours post-dose on lactation day 14.

Grazoprevir: No effects of grazoprevir on growth and postnatal development were observed in nursing pups at up to the highest dose tested *[see Data in (8.1)]*. Maternal systemic exposure (AUC) to grazoprevir was approximately 78 times the exposure in humans at the RHD. Grazoprevir was excreted into the milk of lactating rats following oral administration (up to 400 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations of 54 and 87% that of maternal plasma concentrations observed 2 and 8 hours post-dose, respectively, on lactation day 14.

8.3 Females and Males of Reproductive Potential

If ZEPATIER is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established in pediatric patients less than 18 years of age.

8.5 Geriatric Use

Clinical trials of ZEPATIER with or without ribavirin included 187 subjects aged 65 years and over. Higher elbasvir and grazoprevir plasma concentrations were observed in subjects aged 65 years and over. A higher rate of late ALT elevations was observed in subjects aged 65 years and over in clinical trials *[see Warnings and Precautions (5.1)]*. However, no dosage adjustment of ZEPATIER is recommended in geriatric patients *[see Clinical Pharmacology (12.3)]*.

8.6 Gender

Higher elbasvir and grazoprevir plasma concentrations were observed in females compared to males. Females experienced a higher rate of late ALT elevations in clinical trials *[see Warnings and Precautions (5.1)]*. However, no dose adjustment of ZEPATIER is recommended based on gender *[see Clinical Pharmacology (12.3)]*.

8.7 Race

Higher elbasvir and grazoprevir plasma concentrations were observed in Asians compared to Caucasians. Asians experienced a higher rate of late ALT elevations in clinical trials *[see Warnings and Precautions (5.1)]*. However, no dose adjustment of ZEPATIER is recommended based on race/ethnicity *[see Clinical Pharmacology (12.3)]*.

8.8 Renal Impairment

No dosage adjustment of ZEPATIER is recommended in patients with any degree of renal impairment including patients receiving hemodialysis *[see Clinical Pharmacology (12.3)]*. Administer ZEPATIER with or without ribavirin according to recommendations in Table 1 *[see Dosage and Administration (2.2, 2.3)].* Refer to the prescribing information for ribavirin tablets for renal dosage adjustment of ribavirin in patients with CrCl less than or equal to 50 mL per minute.

8.9 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 hepatic impairment (Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in

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patients with severe hepatic impairment (Child-Pugh C) due to a 12-fold increase in grazoprevir exposure in non-HCV infected Child-Pugh C subjects *[see Dosage and Administration (2.4), Contraindications (4), and Clinical Pharmacology (12.3)].*

The safety and efficacy of ZEPATIER have not been established in patients awaiting liver transplant or in liver transplant recipients.

10 OVERDOSAGE

Human experience of overdose with ZEPATIER is limited. No specific antidote is available for overdose with ZEPATIER. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

Hemodialysis does not remove elbasvir or grazoprevir since elbasvir and grazoprevir are highly bound to plasma protein *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

ZEPATIER is a fixed-dose combination tablet containing elbasvir and grazoprevir for oral administration.

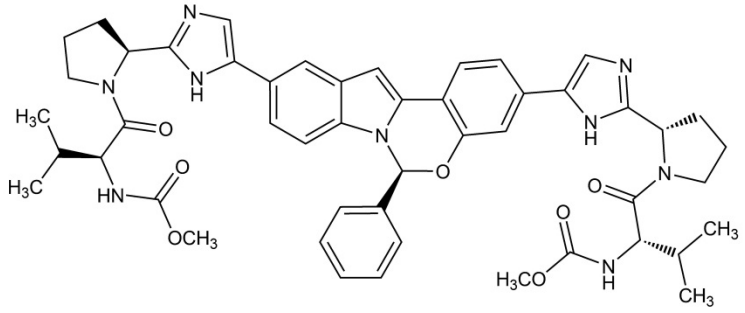
Elbasvir is an HCV NS5A inhibitor, and grazoprevir is an HCV NS3/4A protease inhibitor.

Each tablet contains 50 mg elbasvir and 100 mg grazoprevir. The tablets include the following inactive ingredients: 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, ferrosoferric oxide, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

Elbasvir:

The IUPAC name for elbasvir is Dimethyl *N*,*N'*-([(6*S*)-6-phenylindolo[1,2-*c*][1,3]benzoxazine-3,10-diyl]bis{1*H*-imidazole-5,2-diyl-(2*S*)-pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})dicarbamate.

It has a molecular formula of $C_{49}H_{55}N_9O_7$ and a molecular weight of 882.02. It has the following structural formula:

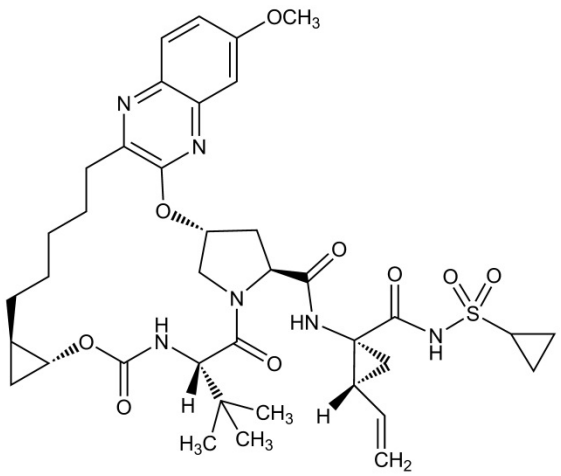


Elbasvir is practically insoluble in water (less than 0.1 mg per mL) and very slightly soluble in ethanol (0.2 mg per mL), but is very soluble in ethyl acetate and acetone.

Grazoprevir:

The IUPAC name for grazoprevir is (1a*R*,5*S*,8*S*,10*R*,22a*R*)-*N*-[(1*R*,2*S*)-1-[(Cyclopropylsulfonamido)carbonyl]-2-ethenylcyclopropyl]-14-methoxy-5-(2-methylpropan-2-yl)-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide.

It has a molecular formula of $C_{38}H_{50}N_6O_9S$ and a molecular weight of 766.90. It has the following structural formula:



Grazoprevir is practically insoluble in water (less than 0.1 mg per mL) but is freely soluble in ethanol and some organic solvents (e.g., acetone, tetrahydrofuran and N,N-dimethylformamide).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZEPATIER is a fixed-dose combination of elbasvir and grazoprevir which are direct-acting antiviral agents against the hepatitis C virus *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

Cardiac Electrophysiology

Thorough QT studies have been conducted for elbasvir and grazoprevir.

The effect of elbasvir 700 mg on QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) 3-period crossover thorough QT trial in 42 healthy subjects. At a concentration 3 to 4 times the therapeutic concentration, elbasvir does not prolong QTc to any clinically relevant extent.

The effect of grazoprevir 1600 mg (16 times the approved dose) on QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) 3-period crossover thorough QT trial in 41 healthy subjects. At a concentration 40 times the therapeutic concentration, grazoprevir does not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetic properties of elbasvir and grazoprevir have been evaluated in non-HCV-infected adult subjects and in HCV-infected adult subjects. Elbasvir pharmacokinetics were similar in healthy subjects and HCV-infected subjects and were approximately dose-proportional over the range of 5-100 mg once daily. Grazoprevir oral exposures are approximately 2-fold greater in HCV-infected subjects as compared to healthy subjects. Grazoprevir pharmacokinetics increased in a greater than dose-proportional manner over the range of 10-800 mg once daily in HCV-infected subjects. Ribavirin co-administration with ZEPATIER had no clinically relevant impact on plasma AUC and C_{max} of elbasvir and grazoprevir compared to administration of ZEPATIER alone. The geometric mean steady-state pharmacokinetic parameter values for elbasvir and grazoprevir in non-cirrhotic HCV-infected subjects are provided in Table 7. Following once daily administration of ZEPATIER to HCV-infected subjects, elbasvir and grazoprevir reached steady state within approximately 6 days.

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Table 7: Geometric Mean (90% Confidence Interval) for Elbasvir and Grazoprevir Steady State Pharmacokinetic Parameter Values in Non-Cirrhotic HCV-Infected Subjects Estimated Based on Population Pharmacokinetic Modeling

	Geometric Mean (90% Confidence Interval)		
	AUC_{0-24} (ng•hr/mL)	**C_{max} (ng/mL)**	**C_{24} (ng/mL)**
Elbasvir	1920 (1880, 1960)	121 (118, 123)	48.4 (47.3, 49.6)
Grazoprevir	1420 (1400, 1530)	165 (161, 176)	18.0 (17.8,19.9)

Absorption

Following administration of ZEPATIER to HCV-infected subjects, elbasvir peak concentrations occur at a median T_{max} of 3 hours (range of 3 to 6 hours); grazoprevir peak concentrations occur at a median T_{max} of 2 hours (range of 30 minutes to 3 hours).

Effect of Food

Relative to fasting conditions, the administration of a single dose of ZEPATIER with a high-fat (900 kcal, 500 kcal from fat) meal to healthy subjects resulted in decreases in elbasvir AUC_{0-inf} and C_{max} of approximately 11% and 15%, respectively, and increases in grazoprevir AUC_{0-inf} and C_{max} of approximately 1.5-fold and 2.8-fold, respectively. These differences in elbasvir and grazoprevir exposure are not clinically relevant; therefore, ZEPATIER may be taken without regard to food *[see Dosage and Administration (2.2)]*.

Distribution

Elbasvir and grazoprevir are extensively bound (greater than 99.9% and 98.8%, respectively) to human plasma proteins. Both elbasvir and grazoprevir bind to human serum albumin and α1-acid glycoprotein. Estimated apparent volume of distribution values of elbasvir and grazoprevir are approximately 680 L and 1250 L, respectively, based on population pharmacokinetic modeling.

In preclinical distribution studies, elbasvir distributes into most tissues including the liver; whereas grazoprevir distributes predominantly to the liver likely facilitated by the active transport through the OATP1B1/3 liver uptake transporter.

Elimination

The geometric mean apparent terminal half-life for elbasvir (50 mg) and grazoprevir (100 mg) is approximately 24 and 31 hours, respectively, in HCV-infected subjects.

Metabolism

Elbasvir and grazoprevir are partially eliminated by oxidative metabolism, primarily by CYP3A. No circulating metabolites of either elbasvir or grazoprevir were detected in human plasma.

Excretion

The primary route of elimination of elbasvir and grazoprevir is through feces with almost all (greater than 90%) of radiolabeled dose recovered in feces compared to less than 1% in urine.

Specific Populations

Pediatric Population

The pharmacokinetics of ZEPATIER in pediatric patients less than 18 years of age have not been established.

Geriatric Population

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 16% and 45% higher, respectively, in subjects at least 65 years of age compared to subjects less than 65 years of age.

Gender

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In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 50% and 30% higher, respectively, in females compared to males.

Weight/BMI

In population pharmacokinetic analyses, there was no effect of weight on elbasvir pharmacokinetics. Grazoprevir AUC is estimated to be 15% higher in a 53-kg subject compared to a 77-kg subject. This change is not clinically relevant for grazoprevir.

Race/Ethnicity

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 15% and 50% higher, respectively, for Asians compared to Caucasians. Population pharmacokinetics estimates of exposure of elbasvir and grazoprevir were comparable between Caucasians and Black/African Americans.

Renal Impairment

In population pharmacokinetic analyses, elbasvir AUC was 25% higher in hemodialysis-dependent subjects and 46% higher in non-dialysis-dependent subjects with severe renal impairment compared to elbasvir AUC in subjects without severe renal impairment. In population pharmacokinetic analysis in HCV-infected subjects, grazoprevir AUC was 10% higher in hemodialysis-dependent subjects and 40% higher in non-dialysis-dependent subjects with severe renal impairment compared to grazoprevir AUC in subjects without severe renal impairment. Elbasvir and grazoprevir are not removed by hemodialysis. Elbasvir and grazoprevir are unlikely to be removed by peritoneal dialysis as both are highly protein bound.

Overall, changes in exposure of elbasvir and grazoprevir in HCV-infected subjects with renal impairment with or without hemodialysis are not clinically relevant *[see Use in Specific Populations (8.8)].*

Hepatic Impairment

The pharmacokinetics of elbasvir and grazoprevir were evaluated in non-HCV-infected subjects with mild hepatic impairment (Child-Pugh Category A [CP-A], score of 5-6), moderate hepatic impairment (Child-Pugh Category B [CP-B], score of 7-9) and severe hepatic impairment (Child-Pugh Category C [CP-C], score of 10-15). In addition, the pharmacokinetics of elbasvir and grazoprevir were also evaluated in HCV-infected subjects including CP-A subjects with compensated cirrhosis.

Relative to non-HCV-infected subjects with normal hepatic function, no clinically relevant differences in elbasvir AUC values were observed in non-HCV-infected subjects with mild, moderate, or severe hepatic impairment. In population pharmacokinetic analyses, elbasvir steady-state AUC was similar in HCV-infected subjects with compensated cirrhosis compared to HCV-infected, non-cirrhotic subjects.

Relative to non-HCV-infected subjects with normal hepatic function, grazoprevir AUC values were higher by 1.7-fold, 5-fold, and 12-fold in non-HCV-infected subjects with mild, moderate, and severe hepatic impairment, respectively. In population pharmacokinetic analyses, grazoprevir steady-state AUC values were higher by 1.65-fold in HCV-infected subjects with compensated cirrhosis compared to HCV-infected, non-cirrhotic subjects.

<u>Drug Interaction Studies</u>

Drug interaction studies were performed in healthy adults with elbasvir, grazoprevir, or co-administered elbasvir and grazoprevir and drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions. Table 8 summarizes the effects of co-administered drugs on the exposures of the individual components of ZEPATIER (elbasvir and grazoprevir). Table 9 summarizes the effects of the individual components of ZEPATIER on the exposures of the co-administered drugs. For information regarding clinical recommendations, *[see Contraindications (4), Warnings and Precautions (5.3), 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 9). Elbasvir inhibited P-gp *in vitro*, but no clinically relevant increases in concentrations of digoxin (a P-gp substrate; see Table 9) 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, and esterases (CES1, CES2, and CatA), 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.

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Table 8: 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_{max}	C24
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)[†]	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[‡]	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)
Rilpivirine	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)
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	14	EBR	1.17 (1.11, 1.24)	1.25 (1.16, 1.35)	1.04 (0.97, 1.12)

		200 mg once daily					
	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)
Acid-Reducing Agent							
Famotidine	20 mg single-dose	EBR 50 mg/ GZR 100 mg single-dose	16	EBR	1.05 (0.92, 1.18)	1.11 (0.98, 1.26)	1.03 (0.91, 1.17)
	20 mg single-dose	EBR 50 mg/ GZR 100 mg single-dose	16	GZR	1.10 (0.95, 1.28)	0.89 (0.71, 1.11)	1.12 (0.97, 1.30)
Pantoprazole	40 mg once daily	EBR 50 mg/ GZR 100 mg single-dose	16	EBR	1.05 (0.93, 1.18)	1.02 (0.92, 1.14)	1.03 (0.92, 1.17)
	40 mg once daily	EBR 50 mg/ GZR 100 mg single-dose	16	GZR	1.12 (0.96, 1.30)	1.10 (0.89, 1.37)	1.17 (1.02, 1.34)
Phosphate Binder							
Calcium acetate	2668 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	EBR	0.92 (0.75, 1.14)	0.86 (0.71, 1.04)	0.87 (0.70, 1.09)
	2668 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	GZR	0.79 (0.68, 0.91)	0.57 (0.40, 0.83)	0.77 (0.61, 0.99)
Sevelamer carbonate	2400 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	EBR	1.13 (0.94, 1.37)	1.07 (0.88, 1.29)	1.22 (1.02, 1.45)
	2400 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	GZR	0.82 (0.68, 0.99)	0.53 (0.37, 0.76)	0.84 (0.71, 0.99)
Statin							
Atorvastatin	20 mg single-dose	GZR 200 mg once daily	9	GZR	1.26 (0.97, 1.64)	1.26 (0.83, 1.90)	1.11 (1.00, 1.23)

Pitavastatin	1 mg single-dose	GZR 200 mg once daily	9	GZR	0.81 (0.70, 0.95)	0.72 (0.57, 0.92)	0.91 (0.82, 1.01)
Pravastatin	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	EBR	0.98 (0.93, 1.02)	0.97 (0.89, 1.05)	0.97 (0.92, 1.02)
	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	GZR	1.24 (1.00, 1.53)	1.42 (1.00, 2.03)	1.07 (0.99, 1.16)
Rosuvastatin	10 mg single-dose	EBR 50 mg + GZR 200 mg single-dose	11	EBR	1.09 (0.98, 1.21)	1.11 (0.99, 1.26)	0.96 (0.86, 1.08)
	10 mg single-dose	GZR 200 mg once daily	11	GZR	1.16 (0.94, 1.44)	1.13 (0.77, 1.65)	0.93 (0.84, 1.03)
	10 mg single-dose	EBR 50 mg + GZR 200 mg once daily	11	GZR	1.01 (0.79, 1.28)	0.97 (0.63, 1.50)	0.95 (0.87, 1.04)

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.

*$AUC_{0\text{-}inf}$ for single-dose, $AUC_{0\text{-}24}$ for once daily.

†$AUC_{0\text{-}24}$

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

Table 9: 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_{max}	C_{trough}[†]
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)[‡]	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	EBR	50 mg once daily	9	1.02 (0.93, 1.13)	1.02 (0.92, 1.13)	1.07 (0.97, 1.18)

	daily						
	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 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)[§]
	Raltegravir 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 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 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 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 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 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)
Immunosuppressant							
Cyclosporine	Cyclosporine 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)[§]
Mycophenolic acid	Mycophenolate mofetil 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 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 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 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)[§]
Oral Contraceptive							
Ethinyl estradiol (EE)	0.03 mg EE/ 0.15 mg LNG 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 (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 8 mg/Naloxone 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 8-24 mg/ Naloxone 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 20-120 mg 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 20-150 mg once daily	GZR	200 mg once daily	12	1.09 (1.02, 1.17)	1.03 (0.96, 1.11)	--
S-Methadone	Methadone 20-120 mg 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 20-150 mg once daily	GZR	200 mg once daily	12	1.23 (1.12, 1.35)	1.15 (1.07, 1.25)	--
Statin							
Atorvastatin	Atorvastatin 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 1 mg single-dose	GZR	200 mg once daily	9	1.11 (0.91, 1.34)	1.27 (1.07, 1.52)	--
Pravastatin	Pravastatin 40 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	1.33 (1.09, 1.64)[¶]	1.28 (1.05, 1.55)	--
Rosuvastatin	Rosuvastatin 10 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	2.26 (1.89, 2.69)[#]	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

*$AUC_{0\text{-}inf}$ for single-dose administration; $AUC_{0\text{-}24}$ for once daily administration; $AUC_{0\text{-}12}$ for twice daily administration

[†]C24 for once daily administration; C12 for twice daily administration.

[‡]N=14
[§]C12
[¶]N=10
[#]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_{50} values of 7 pM, 4 pM, and 62 pM, respectively.

Antiviral Activity

In HCV replicon assays, the EC_{50} 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_{50} 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_{50} 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_{50} 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

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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 10. 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 10: 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 N = 37	Genotype 1b N = 8	Genotype 4 N = 5
NS5A	M28A/G/T, Q30H/K/R/Y, L31F/M/V, H58D, Y93H/N/S	L28M, L31F/V, Y93H	L28S/T, M31I/V, P58D, Y93H
NS3	V36L/M, Y56H, V107I, R155I/K, A156G/T/V, V158A, D168A/G/N/V/Y	Y56F, V107I, A156T	A156M/T/V, D168A/G, 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.

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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 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 11), 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 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 11: SVR12 in HCV Genotype 1a-Infected Subjects without or with Baseline NS5A Polymorphisms

NS5A Polymorphism Status	ZEPATIER 12 Weeks SVR12 % (n/N)	ZEPATIER + RBV 16 Weeks SVR12 % (n/N)
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 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.

Genotype 1b

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

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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 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 12. 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 12: Trials Conducted with ZEPATIER

Trial	Population	Study Groups and Duration (Number of Subjects Treated)
C-EDGE TN (double-blind)	GT 1, 4 TN with or without cirrhosis	• ZEPATIER for 12 weeks (N=306) • Placebo for 12 weeks (N=102)
C-EDGE COINFECTION (open-label)	GT 1, 4 TN with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER for 12 weeks (N=217)
C-SURFER (double-blind)	GT 1 TN or TE with or without cirrhosis Severe Renal Impairment including Hemodialysis	• EBR* + GZR* for 12 weeks (N=122) • Placebo for 12 weeks (N=113)
C-SCAPE (open-label)	GT 4 TN without cirrhosis	• EBR* + GZR* for 12 weeks (N=10) • EBR* + GZR* + RBV for 12 weeks (N=10)
C-EDGE TE (open-label)	GT 1, 4 TE with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER for 12 or 16 weeks (N=105, and 101, respectively) • ZEPATIER + RBV for 12 or 16 weeks (N=104 and 104, respectively)
C-SALVAGE (open-label)	GT 1 TE with HCV protease inhibitor regimen† with or without cirrhosis	• EBR* + GZR* + RBV for 12 weeks (N=79)

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.

Reference ID: 3879275

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^2; 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 per m^2; 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 13 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 13: 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 (Immediate Treatment Group)**	**C-EDGE COINFECTION (HCV/HIV-1 Co-Infection)**
Regimen	**ZEPATIER 12 Weeks N=288**	**ZEPATIER 12 Weeks 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 11*.
§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^2; 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 14. 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 14: 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 12 weeks N=96	ZEPATIER + RBV 16 weeks 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 11*.
[§]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^2; 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^2) or CKD Stage 5 (eGFR <15 mL/min/1.73 m^2), 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 15.

Table 15: 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 12 weeks (Immediate Treatment Group) N=122*
Overall SVR	94% (115/122)[†]
Outcome for subjects without SVR	
On-treatment Virologic Failure	0% (0/122)
Relapse	<1% (1/122)
Other[‡]	5% (6/122)
SVR by Genotype	
GT 1a	97% (61/63)
GT 1b[§]	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.
[†]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.
[‡]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
[§]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).

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 (5.2)]*.

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 (5.1) 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 (5.3), 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.

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

Manufactured by:
MSD International GmbH, Ballydine, Clonmel, Ireland

For patent information: www.merck.com/product/patent/home.html

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uspi-mk5172a-t-1601r000

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 ZEPATIER™?

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.

It is not known if ZEPATIER is safe or effective in children under 18 years old, people awaiting a liver transplant, or people who have had a liver transplant.

Who should not take ZEPATIER?

Do not take ZEPATIER if you have certain liver problems.

What should I tell my healthcare provider before taking ZEPATIER?

Tell your healthcare provider if you:

- 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
- have any other medical conditions
- 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.**

Reference ID: 3879275

Are you taking other medicines?

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?

- **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?

- 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.

Reference ID: 3879275

What are the possible side effects of 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
- yellowing of your skin or eyes
- color changes in your stool

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?

- 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.

Reference ID: 3879275

General information about ZEPATIER

- 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.

What are the ingredients in ZEPATIER?

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, ferrosoferric oxide, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

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

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MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
Manufactured by:
MSD International GmbH, Ballydine, Clonmel, Ireland
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Zepatier™
(elbasvir and grazoprevir) tablets

50 mg/100 mg

Rx only

28 Tablets

This carton contains a total of 28 tablets packaged within 2 dose packs.
Each dose pack contains 14 blister units with one tablet per blister unit.

Zepatier™
(elbasvir and grazoprevir) tablets
50 mg/100 mg

Zepatier™
(elbasvir and grazoprevir) tablets
50 mg/100 mg

Each tablet contains 50 mg elbasvir and 100 mg grazoprevir.

Usual Dosage: See Package Insert.

Store 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).

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

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Whitehouse Station, NJ 08889, USA

Manufactured by:
MSD International GmbH
Ballydine, Clonmel, Ireland

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To learn more about Zepatier™
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NDC 0006-3074-01

Zepatier™
(elbasvir and grazoprevir) tablets

50 mg/100 mg

For Position Only
Do Not Scan Barcode

Each tablet contains 50 mg elbasvir and 100 mg grazoprevir.

Usual Dosage: See Package Insert.

Store 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).

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

Rx only

14 Tablets

Lift Here To Open

Lot and Expiration information will be included here.
The Lot and Expiration information will be printed online.

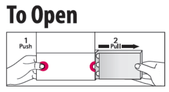
How to use this package

Organized by days of the week, our package design helps you remember to take your pill every day. All the pills in this package are the same.

- **Take 1 pill every day.**
- Take your first pill today, whatever day it happens to be.
- After that, take 1 pill every day at the same time each day until you finish the package.
- This package will last you for 2 weeks (14 days).

Prescribing Information/
Patient Information

To Open



1. Push and Hold

Use thumb to push the button gently, and hold button.

2. Pull

While holding the button down, pull out card.

Zepatier™ (elbasvir and grazoprevir) tablets — **50 mg/100 mg**

Product QR Code
to be placed in
white square area.

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To learn more about Zepatier

XXXXXXXXXX

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Zepatier™ (elbasvir and grazoprevir) tablets — **50 mg/100 mg**

Zepatier™
(elbasvir and grazoprevir) tablets
50 mg/100 mg

Bar prints 100mm @ 100%

(S) (4)

MERCK PROFILE

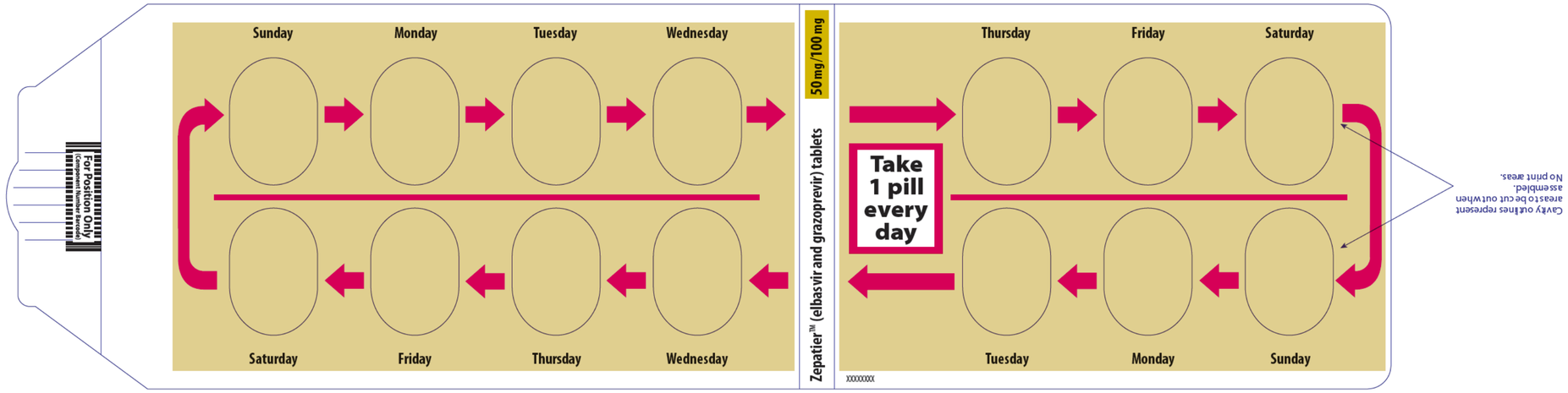
Profile: WI_WAL_105.79mm x 12.70mm x 192.63mm
Profile Revision: 0
Profile Revision Date: 171114
Dimensions (mm): 105.79 x 12.70 x 192.63

Over Sticker | Varnish Free | Text Free
Plant Code | Braille Grid | Tamper Evident
Profile | Perforation | Fold

Reference ID: 3879275

Bar prints 100mm @ 100%

(b) (4)



MERCK PROFILE

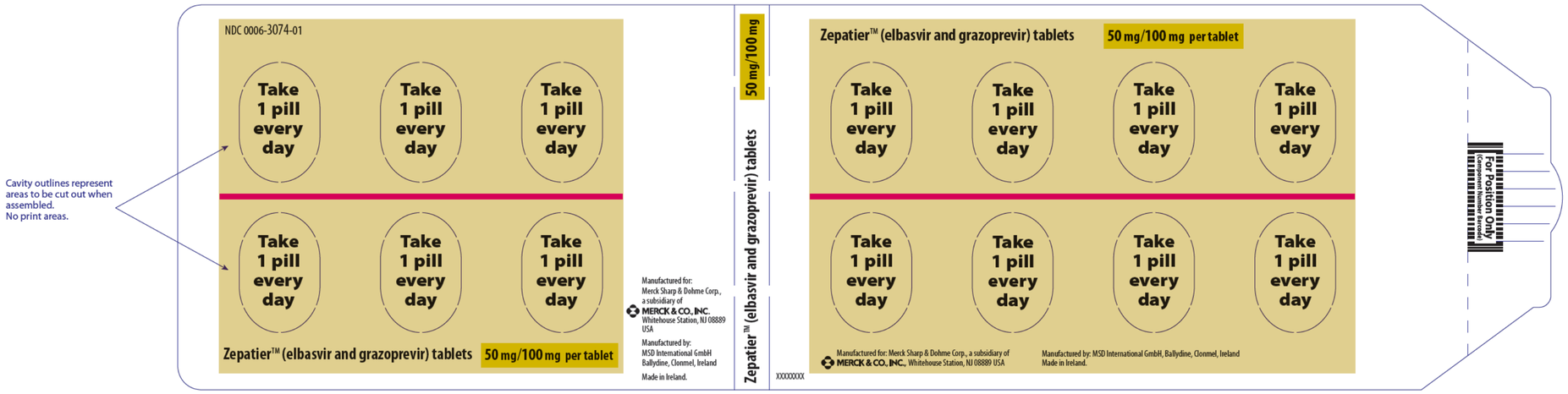
Profile:	WI_WAL_105.00mm x 9.53mm x 190.25mm_Inner
Profile Revision:	1
Profile Revision Date:	050615
Dimensions (mm):	105 x 9.53 x 190.25

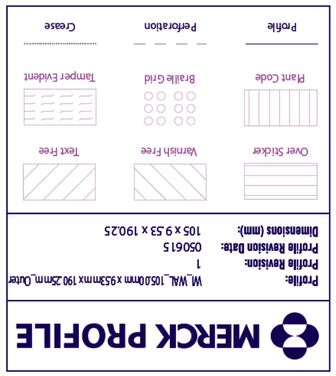
Over Sticker | Varnish Free | Text Free

Plant Code | Braille Grid | Tamper Evident

Profile | Perforation | Crease

Reference ID: 3879275


Cavity outlines represent areas to be cut out when assembled.
No print areas.
NDC 0006-3074-01
Take 1 pill every day
Zepatier™ (elbasvir and grazoprevir) tablets
50 mg/100 mg per tablet
Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC. Whitehouse Station, NJ 08889 USA
Manufactured by: MSD International GmbH Ballydine, Clonmel, Ireland
Made in Ireland.
50 mg/100 mg
Zepatier™ (elbasvir and grazoprevir) tablets
XXXXXXXX
Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889 USA
Manufactured by: MSD International GmbH, Ballydine, Clonmel, Ireland
Made in Ireland.
For Position Only
(Component Number Barcode)


MERCK PROFILE
Profile: WI_WAI_1050mm x 953mm x 190.25mm_Outer
Profile Revision: 1
Profile Revision Date: 050615
Dimensions (mm): 105 x 9.53 x 190.25
Over Sticker
Varnish Free
Text Free
Plant Code
Braille Grid
Tamper Evident
Profile
Perforation
Crease

(b) (4)

Bar prints 100mm @ 100%

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/s/

EDWARD M COX
01/28/2016