ZEPATIER (elbasvir and grazoprevir)

Film-Coated Tablet

1. INDICATIONS AND USAGE

ZEPATIER is indicated for the treatment of chronic hepatitis C (CHC) genotypes 1 (1a and 1b) infection in adults.

2. DOSAGE AND ADMINISTRATION

2.1 General

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.

2.2 Adults

Treatment Regimen and Duration of Therapy

Table 1 below provides the recommended ZEPATIER treatment regimen and duration based on the patient population and genotype in hepatitis C virus (HCV) mono-infected and HCV/HIV-1 co-infected patients with or without cirrhosis.

Table 1: Recommended Dosage Regimens and Durations for ZEPATIER for Treatment of Chronic Hepatitis C Infection in Patients with or without Cirrhosis

Treatment*	Duration
Treatment-Naïve or Treatment-Experienced† Relapsers - Genotype 1a or 1b	
ZEPATIER	12 weeks
Treatment-Experienced† On-Treatment Virologic Failures¶ - Genotype 1a or 1b	
Genotype 1b ZEPATIER	12 weeks
Genotype 1a ZEPATIER with ribavirin #,Þ	16 weeks

*Refer to the prescribing information of the medicinal products that are used in combination with ZEPATIER for specific dosing instructions.

†Genotype 1a or 1b patients who have failed treatment with peginterferon alfa + ribavirin or genotype 1 patients who failed peginterferon alfa + ribavirin + boceprevir, simeprevir, or telaprevir.

¶On-treatment virologic failures are patients who have had a null response, partial response, virologic breakthrough or rebound, or intolerance to prior treatment.

#In clinical trials, the dose of ribavirin was weight-based (<66 kg = 800 mg/day, 66 to 80 kg = 1000 mg/day, 81 to 105 kg = 1200 mg/day, >105 kg = 1400 mg/day) administered in two divided doses with food. For further information on ribavirin dosing and dose modifications, refer to the ribavirin prescribing information.

ÞPatients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73 m^2) or with end stage renal disease (ESRD) should receive ZEPATIER without ribavirin *[see 2 DOSAGE AND ADMINISTRATION, 2.5 Renal Impairment]*.

Missed Dose

In case a dose of ZEPATIER is missed and it is within 16 hours of the time ZEPATIER is usually taken, the patient should be instructed to take ZEPATIER as soon as possible and then take the next dose of ZEPATIER at the usual time. If more than 16 hours have passed since ZEPATIER is usually taken, then the patient should be instructed that the missed dose should NOT be taken and to take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

2.3 Pediatric Patients

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

2.4 Geriatric Patients

No dosage adjustment of ZEPATIER is recommended in geriatric patients *[see 6 USE IN SPECIFIC POPULATIONS, 6.5 Geriatric Use].*

2.5 Renal Impairment

In genotype 1 patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or with ESRD, including patients on dialysis, administer ZEPATIER without ribavirin according to the treatment duration in Table 1 *[see 6 USE IN SPECIFIC POPULATIONS, 6.8 Renal Impairment]*. In genotype 1a patients with severe renal impairment or with ESRD who experienced on treatment-failure during prior peginterferon alfa + ribavirin or interferon only treatment, 12 weeks treatment duration of ZEPATIER may be considered.

2.6 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 a lack of clinical safety and efficacy experience in this patient population and the expected increase in grazoprevir plasma concentration. ZEPATIER is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to the expected significant increase in grazoprevir plasma concentration *[see 3 CONTRAINDICATIONS, and 6 USE IN SPECIFIC POPULATIONS, 6.9 Hepatic Impairment].*

2.7 HCV/HBV (Hepatitis B Virus) Co-Infection

The safety and efficacy of ZEPATIER have not been studied in HCV/HBV co-infected patients. For dosing recommendations of HBV medicinal products, *see 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.4 Drugs without Clinically Significant Interactions with ZEPATIER.*

3. CONTRAINDICATIONS

ZEPATIER is contraindicated in patients with known hypersensitivity to elbasvir, grazoprevir, or any of its components.

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.

ZEPATIER is contraindicated with medicines that inhibit organic anion transporting polypeptide 1B (OATP1B), that are known or expected to significantly increase grazoprevir plasma concentrations, such as atazanavir, darunavir, lopinavir, saquinavir, tipranavir, or cyclosporine, due to the increased risk of ALT elevations *[see 4. WARNINGS AND PRECAUTIONS, 4.4 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions and 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS]*.

ZEPATIER is contraindicated with medicines that are strong inducers of cytochrome P450 3A (CYP3A), such as phenytoin, carbamazepine, or St. John's wort *(Hypericum perforatum),* or with efavirenz due to the expected significant decreases in elbasvir and grazoprevir plasma concentrations and the loss of virologic response *[see 4. WARNINGS AND PRECAUTIONS, 4.4 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions and 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS]*.

ZEPATIER is contraindicated with rifampin because of an initial significant increase in grazoprevir plasma concentration on coadministration (due to OATP1B inhibition), followed by decreases in elbasvir and grazoprevir plasma concentrations during continued coadministration (due to strong CYP3A induction).

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.

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comment*
Antibiotics	Nafcillin	May lead to loss of virologic response to ZEPATIER due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction.
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.
Endothelin Antagonist	Bosentan	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† Etravirine	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.
Stimulants	Modafinil	May lead to loss of virologic response to ZEPATIER due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction.

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

†Efavirenz is included as a strong CYP3A inducer in this table, since co-administration reduced grazoprevir exposure by ≥80% *[see* Table 11*]*.

4. WARNINGS AND PRECAUTIONS

4.1 Risk of Hepatitis B Virus Reactivation in Patients Co-infected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV co-infected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure and death. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and hepatitis B core antibody (anti-HBc) positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct acting antivirals may be increased in these patients.

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

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

4.2 Increased Risk of ALT Elevations

During clinical trials with ZEPATIER with or without ribavirin, <1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in females (2% [11/652]), Asians (2% [4/165]), and subjects aged ≥65 years (2% [3/187]) *[see 7 ADVERSE REACTIONS, 7.1 Clinical Trials Experience]*.

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

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

4.3 Risks Associated with Ribavirin Combination

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 list of warnings and precautions for ribavirin.

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

Co-administration of ZEPATIER and OATP1B inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations is contraindicated *[see 3 CONTRAINDICATIONS and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 Effects of Other Drugs on ZEPATIER]*.

The concomitant use of ZEPATIER and strong CYP3A inducers or efavirenz may significantly decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced therapeutic effect of ZEPATIER. Therefore, the use of ZEPATIER with strong CYP3A inducers or efavirenz is contraindicated *[see 3 CONTRAINDICATIONS and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 Effects of Other Drugs on ZEPATIER]*.

The concomitant use of ZEPATIER and moderate CYP3A inducers may decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced therapeutic effect of ZEPATIER. Therefore, the use of ZEPATIER with moderate CYP3A inducers is not recommended *[see 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 Effects of Other Drugs on ZEPATIER and Table 2]*.

The concomitant use of ZEPATIER and strong CYP3A inhibitors increases elbasvir and grazoprevir concentrations. Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended *[see 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 Effects of Other Drugs on ZEPATIER and Table 3]*.

See Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Established and Other Potential Drug Interactions]*. Consider the potential for drug interactions prior to and during ZEPATIER therapy; review concomitant medications during ZEPATIER therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 Effects of Other Drugs on ZEPATIER, and 5.3 Established and Other Potential Drug Interactions]*.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

[See also 3 CONTRAINDICATIONS, and 4 WARNINGS AND PRECAUTIONS, 4.4 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions.]

As ZEPATIER contains elbasvir and grazoprevir, interactions that have been identified with these agents individually may occur with ZEPATIER.

5.1 Effects of Other Drugs on ZEPATIER

Grazoprevir is a substrate of OATP1B drug transporters. Co-administration of ZEPATIER with OATP1B inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations is contraindicated *[see 3 CONTRAINDICATIONS]*.

Elbasvir and grazoprevir are substrates of CYP3A and P-gp. Co-administration of inducers of CYP3A or P-gp with Zepatier is contraindicated because it may significantly decrease elbasvir and grazoprevir plasma concentrations, which may lead to reduced therapeutic effect of ZEPATIER.

Co-administration of ZEPATIER with strong CYP3A inhibitors increases elbasvir and grazoprevir plasma concentrations. Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended *[see 4 WARNINGS AND PRECAUTIONS, 4.4 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions, and Table 2]*. Co-

administration of ZEPATIER with P-gp inhibitors is expected to have a minimal effect on the plasma concentrations of ZEPATIER.

The potential for grazoprevir to be a breast cancer resistance protein (BCRP) substrate cannot be excluded.

5.2 Effects of ZEPATIER on Other Drugs

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. Elbasvir is not a CYP3A inhibitor *in vitro* and grazoprevir is a weak, but not clinically relevant, CYP3A inhibitor in humans. Therefore, no dose adjustment is required for CYP3A substrates when co-administered with ZEPATIER.

Elbasvir has minimal intestinal P-gp inhibition in humans and grazoprevir is not a P-gp inhibitor *in vitro.* Therefore, P-gp substrates may be administered without dose adjustment when co-administered with ZEPATIER. Elbasvir and grazoprevir are not OATP1B inhibitors in humans. Clinically significant drug interactions with ZEPATIER as an inhibitor of other CYP enzymes, UGT1A1, esterases (CES1, CES2, and CatA), organic anion transporters (OAT)1 and OAT3, and organic cation transporter (OCT)2 are not expected, and multiple-dose administration of elbasvir or grazoprevir is unlikely to induce the metabolism of drugs metabolized by CYP isoforms based on *in vitro* data.

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

Patients treated with vitamin K antagonists

Frequent monitoring of relevant laboratory parameters (e.g., International Normalized Ratio [INR] in patients taking vitamin K antagonists, blood glucose levels in diabetic patients) or drug concentrations of concomitant medications such as CYP3A substrates with a narrow therapeutic index (e.g., certain immunosuppressants) is recommended to ensure safe and effective use. Dose adjustments of concomitant medications may be necessary.

5.3 Established and Other Potential 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 3 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 4 WARNINGS AND PRECAUTIONS, 4.4 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions]*. An up "↑" or down "↓" arrow represents a change in exposure that requires monitoring or a dose adjustment of that medication, or the co-administration is not recommended or contraindicated. No clinically relevant change in exposure is represented by a horizontal arrow "↔". The table is not all inclusive.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels. (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
ACID REDUCING AGENTS		
H2-receptor antagonists		
Famotidine (20 mg single dose)/ elbasvir (50 mg single dose)/ grazoprevir (100 mg single dose)	↔ Elbasvir ↔ Grazoprevir	No dose adjustment is required.
Proton pump inhibitors		
Pantoprazole (40 mg once daily)/ elbasvir (50 mg single dose)/ grazoprevir (100 mg single dose)	↔ Elbasvir ↔ Grazoprevir	No dose adjustment is required.
Antacids		
Aluminium or magnesium hydroxide; calcium carbonate	Interaction not studied. Expected: ↔ Elbasvir ↔ Grazoprevir	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
ANTIARRHYTHMICS		
Digoxin (0.25 mg single dose)/ elbasvir (50 mg once daily)	↔ Digoxin (P-gp inhibition)	No dose adjustment is required.
ANTIBIOTICS		
Nafcillin	Interaction not studied. Expected: ↓ Elbasvir ↓ Grazoprevir (CYP3A induction)	Co-administration is contraindicated.
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied. Expected: ↑ Dabigatran (P-gp inhibition)	Concentrations of dabigatran may increase when co-administered with elbasvir, with possible increased bleeding risk. Clinical and laboratory monitoring is recommended.
Vitamin K antagonists	Interaction not studied.	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with ZEPATIER.
ANTICONVULSANTS		
Carbamazepine Phenytoin	Interaction not studied. Expected: ↓ Elbasvir ↓ Grazoprevir (CYP3A or P-gp induction)	Co-administration is contraindicated.
ANTIFUNGALS		
Ketoconazole		
(400 mg PO once daily)/ elbasvir (50 mg single dose)	↔ Elbasvir	Co-administration is not recommended.

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
(400 mg PO once daily)/ grazoprevir (100 mg single dose)	↑ Grazoprevir (CYP3A inhibition)	
ANTIMYCOBACTERIALS		
Rifampicin		
(600 mg IV single dose)/ elbasvir (50 mg single dose)	↔ Elbasvir	Co-administration is contraindicated.
(600 mg IV single dose)/ grazoprevir (200 mg single dose)	↑ Grazoprevir (OATP1B inhibition)	
(600 mg PO single dose)/ elbasvir (50 mg single dose)	↔ Elbasvir	
(600 mg PO single dose)/ grazoprevir (200 mg once daily)	↑ Grazoprevir (OATP1B inhibition)	
(600 mg PO once daily)/ grazoprevir (200 mg once daily)	↔ Grazoprevir (OATP1B inhibition and CYP3A induction)	
ASTHMA AGENTS		
Montelukast (10 mg single dose)/ grazoprevir (200 mg single dose)	↔ Montelukast	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
ENDOTHELIN ANTAGONIST		
Bosentan	Interaction not studied. Expected: ↓ Elbasvir ↓ Grazoprevir (CYP3A or P-gp induction)	Co-administration is contraindicated.
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg single dose sofosbuvir)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Sofosbuvir ↔ GS-331007	No dose adjustment is required.
HERBAL SUPPLEMENTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied. *Expected:* ↓ Elbasvir ↓ Grazoprevir (CYP3A or P-gp induction)	Co-administration is contraindicated.
HBV AND HIV ANTIVIRAL AGENTS: NUCLEOS(T)IDE REVERSE TRANSCRIPTASE INHIBITORS		
Tenofovir disoproxil fumarate		
(300 mg once daily)/ elbasvir (50 mg once daily)	↔ Elbasvir ↔ Tenofovir	No dose adjustment is required.
(300 mg once daily)/ grazoprevir (200 mg once daily)	↔ Grazoprevir ↔ Tenofovir	

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
(300 mg once daily)/elbasvir (50 mg once daily)/grazoprevir (100 mg once daily)	↔ Tenofovir	
Lamivudine Abacavir Entecavir	Interaction not studied. *Expected:* ↔ Elbasvir ↔ Grazoprevir ↔ Lamivudine ↔ Abacavir ↔ Entecavir	No dose adjustment is required.
Emtricitabine (200 mg once daily)	Interaction studied with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (fixed-dose combination) ↔ Emtricitabine	
HIV ANTIVIRAL AGENTS: PROTEASE INHIBITORS		
Atazanavir/ritonavir		Co-administration is contraindicated.
(300 mg once daily)/ ritonavir (100 mg once daily/ elbasvir (50 mg once daily)	↑ Elbasvir (combination of mechanisms including CYP3A inhibition) ↔ Atazanavir	
(300 mg once daily)/ ritonavir (100 mg once daily/ grazoprevir (200 mg once daily)	↑ Grazoprevir (combination of OATP1B and CYP3A inhibition) ↔ Atazanavir	

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
Darunavir/ritonavir		
(600 mg twice daily)/ ritonavir (100 mg twice daily/ elbasvir (50 mg once daily)	↔ Elbasvir ↔ Darunavir	
(600 mg twice daily)/ ritonavir (100 mg twice daily/ grazoprevir (200 mg once daily)	↑ Grazoprevir (combination of OATP1B and CYP3A inhibition) ↔ Darunavir	
Lopinavir/ritonavir		
(400 mg twice daily)/ ritonavir (100 mg twice daily/ elbasvir (50 mg once daily)	↑ Elbasvir (combination of mechanisms including CYP3A inhibition) ↔ Lopinavir	
(400 mg twice daily)/ ritonavir (100 mg twice daily/ grazoprevir (200 mg once daily)	↑ Grazoprevir (combination of OATP1B and CYP3A inhibition) ↔ Lopinavir	
Saquinavir/ritonavir Tipranavir/ritonavir Atazanavir	Interaction not studied. *Expected:* ↑ Grazoprevir (combination of mechanisms including CYP3A inhibition)	

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
HIV ANTIVIRAL AGENTS: NON-NUCLEOSIDE HIV REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz		
(600 mg once daily)/ elbasvir (50 mg once daily)	↓ Elbasvir (CYP3A or P-gp induction) ↔ Efavirenz	Co-administration is contraindicated.
(600 mg once daily)/ grazoprevir (200 mg once daily)	↓Grazoprevir (CYP3A or P-gp induction) ↔ Efavirenz	
Etravirine	Interaction not studied. *Expected:* ↓ Elbasvir ↓ Grazoprevir (CYP3A or P-gp induction)	Co-administration is contraindicated.
Rilpivirine (25 mg once daily)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir ↔ Grazoprevir ↔ Rilpivirine	No dose adjustment is required.
HIV ANTIVIRAL AGENTS: INTEGRASE STRAND TRANSFER INHIBITORS		
Dolutegravir (50 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir ↔ Grazoprevir ↔ Dolutegravir	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
Raltegravir		
(400 mg single dose)/ elbasvir (50 mg single dose)	↔ Elbasvir ↔ Raltegravir	No dose adjustment is required.
(400 mg twice daily)/ grazoprevir (200 mg once daily)	↔ Grazoprevir ↔ Raltegravir	
HIV ANTIVIRAL AGENTS: OTHER		
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (fixed-dose combination)		
elvitegravir (150 mg once daily)/cobicistat (150 mg once daily)/ emtricitabine (200 mg once daily)/ tenofovir disoproxil fumarate (300 mg once daily)/elbasvir (50 mg once daily)/ grazoprevir (100 mg once daily)	↑ Elbasvir (CYP3A and OATP1B inhibition) ↑ Grazoprevir (CYP3A and OATP1B inhibition) ↔ Elvitegravir ↔ Cobicistat ↔ Emtricitabine ↔ Tenofovir	Co-administration with ZEPATIER is contraindicated.
HMG-CoA REDUCTASE INHIBITORS		
Atorvastatin		
(20 mg single dose)/ grazoprevir (200 mg once daily)	↑ Atorvastatin (primarily due to intestinal BCRP inhibition) ↔ Grazoprevir	The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER.

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
(10 mg single dose)/ elbasvir (50 mg once daily) / grazoprevir (200 mg once daily)	↑ Atorvastatin	
Rosuvastatin		
(10 mg single dose)/ grazoprevir (200 mg once daily)	↑ Rosuvastatin (intestinal BCRP inhibition) ↔ Grazoprevir	The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with ZEPATIER.
(10 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↑ Rosuvastatin (intestinal BCRP inhibition) ↔ Elbasvir ↔ Grazoprevir	
Fluvastatin Lovastatin Simvastatin	Interaction not studied. *Expected:* ↑ Fluvastatin (primarily due to intestinal BCRP inhibition) ↑ Lovastatin (CYP3A inhibition) ↑ Simvastatin (primarily due to intestinal BCRP inhibition and CYP3A inhibition)	The dose of fluvastatin, lovastatin, or simvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER.
Pitavastatin (1 mg single dose)/ grazoprevir (200 mg once daily)	↔ Pitavastatin ↔ Grazoprevir	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
Pravastatin (40 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Pravastatin ↔ Elbasvir ↔ Grazoprevir	No dose adjustment is required.
IMMUNOSUPPRESSANTS		
Ciclosporin (400 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir ↑ Grazoprevir (due in part to OATP1B and CYP3A inhibition) ↔ Ciclosporin	Co-administration is contraindicated.
Mycophenolate mofetil (1,000 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir ↔ Grazoprevir ↔ Mycophenolic acid	No dose adjustment is required.
Prednisone (40 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily	↔ Elbasvir ↔ Grazoprevir ↔ Prednisone ↔ Prednisolone	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
Tacrolimus (2 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir ↔ Grazoprevir ↑ Tacrolimus (CYP3A inhibition)	Frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of co-administration is recommended.
KINASE INHIBITOR		
Sunitinib	Interaction not studied. *Expected:* ↑ sunitinib (possibly due to intestinal BCRP inhibition)	Co-administration of ZEPATIER with sunitinib may increase sunitinib concentrations leading to an increased risk of sunitinib-associated adverse events. Use with caution; dose adjustment of sunitinib may be required.
OPIOID-SUBSTITUTION THERAPY		
Buprenorphine/naloxone		
(8 mg/2 mg single dose)/ elbasvir (50 mg single dose)	↔ Elbasvir ↔ Buprenorphine ↔ Naloxone	No dose adjustment is required.
(8-24 mg/2-6 mg once daily)/ grazoprevir (200 mg once daily)	↔ Grazoprevir ↔ Buprenorphine	
Methadone		
(20-120 mg once daily)/ elbasvir (50 mg once daily)	↔ R-Methadone ↔ S-Methadone	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
(20-150 mg once daily)/ grazoprevir (200 mg once daily)	↔ R-Methadone ↔ S-Methadone	
ORAL CONTRACEPTIVES		
Ethinyl oestradiol (EE) / Levonorgestrel (LNG)		
(0.03 mg EE/ 0.15 mg LNG single-dose)/ elbasvir (50 mg once daily)	↔ EE ↔ LNG	No dose adjustment is required.
(0.03 mg EE/ 0.15 mg LNG single-dose)/ grazoprevir (200 mg once daily)	↔ EE ↔ LNG	
PHOSPHATE BINDERS		
Calcium acetate (2,668 mg single dose)/ elbasvir (50 mg single dose)/ grazoprevir (100 mg single dose)	↔ Elbasvir ↔ Grazoprevir	No dose adjustment is required.
Sevelamer carbonate (2,400 mg single dose)/ elbasvir (50 mg single dose)/ grazoprevir (100 mg single dose)	↔ Elbasvir ↔ Grazoprevir	

Medicinal product by therapeutic areas	Effects on medicinal product levels. (likely mechanism of interaction)	Recommendation concerning co-administration with ZEPATIER
SEDATIVES		
Midazolam (2 mg single dose)/ grazoprevir (200 mg once daily)	↔ Midazolam	No dose adjustment is required.
STIMULANTS		
Modafinil	Interaction not studied. *Expected:* ↓ Elbasvir ↓ Grazoprevir (CYP3A or P-gp induction)	Co-administration is contraindicated.

5.4 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.

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

6. USE IN SPECIFIC POPULATIONS

If ZEPATIER is co-administered with ribavirin, the information for ribavirin with regard to contraception, pregnancy testing, pregnancy, breastfeeding, and fertility also applies to this combination regimen (refer to the prescribing information of the co-administered medicinal product for additional information).

6.1 Women of Childbearing Potential / Contraception in Males and Females

When ZEPATIER is used in combination with ribavirin, women of childbearing potential or their male partners must use an effective form of contraception during treatment and for a period of time after the treatment has concluded.

6.2 Pregnancy

There are no adequate and well-controlled studies with ZEPATIER in pregnant women. No effects on embryo-fetal development were observed in rats or rabbits at elbasvir or grazoprevir exposures higher than exposures in humans at the recommended clinical dose. Because animal reproduction studies are not always predictive of human response, ZEPATIER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

6.3 Nursing Mothers

There are no human data to assess whether ZEPATIER is excreted in human breast milk. Elbasvir and grazoprevir are excreted in the milk of lactating rats. Concentrations of elbasvir were higher and concentrations of grazoprevir were lower in breast milk than maternal plasma in rats. No effects on postnatal development were observed in nursing rats when lactating dams were exposed to elbasvir or grazoprevir.

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.

6.4 Fertility

No human data on the effect of elbasvir and grazoprevir on fertility are available. No effects on male or female fertility were observed in mature rats at elbasvir and grazoprevir exposures higher than the exposure in humans at the recommended clinical dose.

6.5 Pediatric Use

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

6.6 Geriatric Use

No overall differences in safety or efficacy were observed between subjects aged 65 years and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Higher elbasvir and grazoprevir plasma concentrations were observed in subjects aged 65 years and over. No dosage adjustment of ZEPATIER is recommended in geriatric patients.

6.7 Gender

Higher elbasvir and grazoprevir plasma concentrations were observed in females compared to males. No dose adjustment of ZEPATIER is recommended based on gender.

6.8 Race

Higher elbasvir and grazoprevir plasma concentrations were observed in Asians compared to Whites. No dose adjustment of ZEPATIER is recommended based on race/ethnicity.

6.9 Renal Impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild, moderate, or severe renal impairment. No dosage adjustment of ZEPATIER is recommended in patients who are on dialysis (including hemodialysis or peritoneal dialysis).

In patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or with ESRD, including patients on dialysis, administer ZEPATIER without ribavirin *[see 2 DOSAGE AND ADMINISTRATION, 2.5 Renal Impairment]*.

6.10 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 a lack of clinical safety and efficacy experience in this population and the expected increase in grazoprevir exposure of 5-fold. ZEPATIER is contraindicated in patients with severe hepatic impairment (Child-Pugh C) based on the expected significant increase in grazoprevir exposure of approximately 12-fold *[see 2 DOSAGE AND ADMINISTRATION, 2.6 Hepatic Impairment and 3 CONTRAINDICATIONS]*.

6.11 Other HCV Genotypes

The efficacy of ZEPATIER have not been established in patients infected with HCV genotypes 2, 3, 4, 5 and 6 *[see 1 INDICATIONS AND USAGE]*.

6.12 Effects on Ability to Drive and Use Machines

ZEPATIER (administered alone or in combination with ribavirin) is not likely to have an effect on the ability to drive and use machines. Patients should be informed that fatigue has been reported during treatment with ZEPATIER (see section 4.8).

7. ADVERSE REACTIONS

Summary of the safety profile

The safety of ZEPATIER was assessed based on Phase 2 and 3 clinical studies in approximately 2,000 subjects with chronic hepatitis C infection with compensated liver disease (with or without cirrhosis).

In clinical studies, the most commonly reported adverse reactions (greater than 10%) were fatigue and headache. Less than 1 % of subjects treated with ZEPATIER with or without ribavirin had serious adverse reactions (abdominal pain, transient ischaemic attack and anaemia). Less than 1 % of subjects treated with ZEPATIER with or without ribavirin permanently discontinued treatment due to adverse reactions. The frequency of serious adverse reactions and discontinuations due to adverse reactions in subjects with compensated cirrhosis were comparable to those seen in subjects without cirrhosis.

When elbasvir/grazoprevir was studied with ribavirin, the most frequent adverse reactions to elbasvir/grazoprevir + ribavirin combination therapy were consistent with the known safety profile of ribavirin.

Tabulated summary of adverse reactions

The following adverse reactions were identified in patients taking ZEPATIER without ribavirin for 12 weeks. The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000).

Table 4: Adverse reactions identified with ZEPATIER*

Frequency	Adverse reactions

Metabolism and nutrition disorders :	
Common	decreased appetite
Psychiatric disorders :	
Common	insomnia, anxiety, depression
Nervous system disorders :	
Very common	headache
Common	dizziness
Gastrointestinal disorders :	
Common	nausea, diarrhoea, constipation, upper abdominal pain, abdominal pain, dry mouth, vomiting
Skin and subcutaneous tissue disorders :	
Common	pruritus, alopecia
Musculoskeletal and connective tissue disorders :	
Common	arthralgia, myalgia
General disorders and administration site conditions :	
Very common	fatigue
Common	asthenia, irritability

*Based on pooled data from patients treated with ZEPATIER for 12 weeks without ribavirin

Description of selected adverse reactions

Laboratory abnormalities

Changes in selected laboratory parameters are described in Table 5.

Table 5. Selected treatment emergent laboratory abnormalities

Laboratory Parameters	ZEPATIER* N = 834 n (%)
ALT (IU/L)	
5.1-10.0 x ULN† (Grade 3)	6 (0.7%)
>10.0 x ULN (Grade 4)	6 (0.7%)
Total Bilirubin (mg/dL)	
2.6-5.0 x ULN (Grade 3)	3 (0.4%)
>5.0 x ULN (Grade 4)	0

*Based on pooled data from patients treated with ZEPATIER for 12 weeks without ribavirin

†ULN : Upper limit of normal according to testing laboratory.

Serum Late ALT elevations

During clinical studies with ZEPATIER with or without ribavirin, regardless of treatment duration, < 1 % (13/1,690) 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 4 WARNINGS AND PRECAUTIONS, 4.1 Increased Risk of ALT Elevations]*. The frequency of late ALT elevations was higher in subjects with higher grazoprevir plasma concentration *[see 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 Effects of Other Drugs on ZEPATIER*]. The incidence of late ALT elevations was not affected by treatment duration. Cirrhosis was not a risk factor for late ALT elevations. Less than 1% of subjects treated with ZEPATIER with or without ribavirin experienced ALT elevations >2.5 –5 times the ULN during treatment; there were no treatment discontinuations due to these ALT elevations.

Paediatric population

No data are available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

8. 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.

9. CLINICAL STUDIES

9.1 Overview of Clinical Trials

The safety and efficacy of ZEPATIER or elbasvir + grazoprevir were evaluated in 6 clinical trials in approximately 1700 subjects with chronic hepatitis C (CHC) infection with

compensated liver disease (with and without cirrhosis). An overview of the trials is provided in Table 6.

Table 6: Trials Conducted with ZEPATIER

Trial	Population	Study Arms and Duration (Number of Subjects Treated)
C-EDGE TN (double-blind)	GT 1, 4, 6 TN with or without cirrhosis	• ZEPATIER for 12 weeks (N=316) • Placebo for 12 weeks (N=105)
C-EDGE CO-INFECTION (open-label)	GT 1, 4, 6 TN with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER for 12 weeks (N=218)
C-SURFER (double-blind)	GT 1 TN or TE with or without cirrhosis Chronic Kidney Disease	• EBR* + GZR* for 12 weeks (N=122) • Placebo for 12 weeks (N=113)
C-WORTHY (open-label)	GT 1, 3 TN with or without cirrhosis TE Null Responder with or without cirrhosis TN HCV/HIV-1 co-infection without cirrhosis	• EBR* + GZR* for 8, 12, or 18 weeks (N=31, 136, and 63, respectively) • EBR* + GZR* + RBV† for 8, 12, or 18 weeks (N=60, 152, and 65, respectively)
C-EDGE TE (open-label)	GT 1, 4, 6 TE with or without cirrhosis with or without HCV/HIV-1 co-infection	• ZEPATIER for 12 or 16 weeks (N=105, and 105, respectively) • ZEPATIER + RBV† for 12 or 16 weeks (N=104 and 106, 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 [peg-IFN] 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

†RBV was administered at a total daily dose of 800 mg to 1400 mg based on weight *[see 2 DOSAGE AND ADMINISTRATION, 2.2 Adults]*

‡ Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with peg-IFN + RBV

- C-EDGE TN was a randomized, double-blind, placebo-controlled trial in treatment-naïve subjects with genotype 1, 4, or 6 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).
- C-EDGE CO-INFECTION was an open-label trial in treatment-naïve HCV/HIV-1 co-infected subjects with genotype 1, 4, or 6 infection with or without cirrhosis. Subjects received ZEPATIER for 12 weeks.
- 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 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 peg-IFN ± RBV therapy. Subjects were randomized in a 1:1 ratio to one of the following treatment groups: EBR + GZR 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 PK arm).
- C-WORTHY was a multi-arm, multi-stage, randomized, open-label trial which included subjects with genotype 1 or 3 infection who were treatment-naïve or who had failed prior therapy with peg-IFN ± RBV therapy. In the stage evaluating shorter duration of therapy in subjects with genotype 1b infection without cirrhosis, subjects were randomized in a 1:1 ratio to EBR + GZR with or without RBV for 8 weeks. In the stage evaluating subjects with genotype 3 infection without cirrhosis who were treatment-naïve, subjects were randomized to EBR + GZR with RBV for 12 or 18 weeks. In the other stages, subjects with GT 1 infection with or without cirrhosis who were treatment-naïve (with or without HCV/HIV-1 co-infection) or who were peg-IFN + RBV null responders, were randomized to EBR + GZR with or without RBV for 8, 12 or 18 weeks.
- C-EDGE TE was a randomized, open-label trial in subjects with genotype 1, 4, or 6 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior therapy with peg-IFN + 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.

- C-SALVAGE was an open-label trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with peg-IFN + RBV. Subjects received EBR + GZR + RBV for 12 weeks.

Sustained virologic response 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 (SVR). 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/mL, with the exception of C-WORTHY and C-SCAPE where the assay had an LLOQ of 25 HCV RNA IU/mL.

9.2 Clinical Trials in Treatment-Naïve Subjects with Genotype 1 HCV (C-EDGE TN and C-EDGE CO-INFECTION)

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 CO-INFECTION 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 CO-INFECTION 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 7 presents treatment outcomes for

ZEPATIER in treatment-naïve subjects with genotype 1 infection from C-EDGE TN (immediate treatment group) and C-EDGE CO-INFECTION.

Table 7: C-EDGE TN and C-EDGE CO-INFECTION: 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 CO-INFECTION (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 polymorphism on SVR12, *[see Microbiology (12.4)], Table 11.*

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

9.3 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/m2; 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 8. 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.

Table 8: 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 or baseline NS5A polymorphism on SVR, *[see Microbiology (12.4)], Table11.*

§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/m2; 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.

9.4 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 m2) or CKD Stage 5 (eGFR <15 mL/min/1.73 m2), 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 9.

Table 9: 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 subject 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 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.

10. CLINICAL PHARMACOLOGY

10.1 Therapeutic Class

Direct acting antivirals

10.2 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 10 CLINICAL PHARMACOLOGY, Microbiology]*.

10.3 Pharmacodynamics

Cardiac Electrophysiology

Thorough QT studies have been conducted for elbasvir and grazoprevir.

The effect of elbasvir 700 mg on the 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 plasma concentration 3 to 4 times the therapeutic plasma concentration, elbasvir does not prolong QTc to any clinically relevant extent.

The effect of grazoprevir 1600 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 41 healthy subjects. At a plasma concentration 40 times the therapeutic plasma concentration, grazoprevir does not prolong QTc to any clinically relevant extent.

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 NS3/4A protease enzymes from HCV genotypes 1a, 1b and 4, with IC_{50} values ranging from 4 to 62 pM.

Antiviral Activity

In HCV replicon assays, the EC_{50} values of elbasvir against full-length replicons from genotypes 1a, 1b, and 4, 0.004 nM, 0.003 nM, and 0.0003 nM, respectively. The median EC_{50} values of elbasvir against chimeric replicons encoding NS5A sequences from clinical isolates were 0.005 nM for genotype 1a (range 0.003-0.009 nM; N=5), 0.009 nM for genotype 1b (range 0.005-0.010 nM; N=4), and 0.0007 nM for genotype 4 (range 0.0002-34 nM; N=14).

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), and 0.2 nM for genotype 4 (range 0.11-0.33 nM; N=5).

Evaluation of elbasvir in combination with grazopreviror 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.

For elbasvir, in HCV genotype 1a replicons, single NS5A substitutions Q30D/E/H/R, L31M/V and Y93C/H/N reduced elbasvir antiviral activity by 6- to 2000-fold. In genotype 1b replicons, single NS5A substitutions L31F and Y93H reduced elbasvir antiviral activity by 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 D168A/E/G/S/V reduced grazoprevir antiviral activity by 2- to 81-fold. In genotype 1b replicons, single NS3 substitutions F43S, A156S/T/V, and D168A/G/V reduced grazoprevir antiviral activity by 2- 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 genotype 1a or 1b subjects treated with regimens containing ZEPATIER or elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical trials, resistance analyses were conducted for 45 subjects who experienced virologic failure and had sequence data available (4 with on-treatment virologic failure, 41 with post-treatment relapse).

Treatment-emergent substitutions observed in the viral populations of these subjects based on genotypes are shown in Table 10.

Table 10: Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of ZEPATIER with and without Ribavirin Regimens in Phase 2 and Phase 3 Clinical Trials

Target	Emergent Amino Acid Substitutions	Genotype 1a N = 37 % (n)	Genotype 1b N = 8 % (n)
NS5A	Any of the following NS5A substitutions: M/L28A/G/T/S* Q30H/K/R/Y, L/M31F/M/I/V, H/P58D, Y93H/N/S	81% (30)	88% (7)
	M/L28A/G/T/S	19% (7)	13% (1)
	Q30H/K/Y	14% (5)	--
	Q30R	46% (17)	--
	L/M31M/F/I/V†	11% (4)	25% (2)
	H/P58D‡	5% (3)	--
	Y93H/N/S	14% (5)	63% (5)
NS3	Any of the following NS3 substitutions: V36L/M, Y56F/H, V107I, R155I/K, A156G/M/T/V, V158A, D168A/C/E/G/N/V/Y, V170I	78% (29)	25% (2)
	V36L/M	11% (4)	--
	Y56F/H	14% (5)	13% (1)
	V107I	3% (1)	13% (1)
	R155I/K	5% (2)	--
	A156T	27% (10)	13% (1)
	A156G/V/M	8% (3)	--
	V158A	5% (2)	--
	D168A	35% (13)	--
	D168C/E/G/N/V/Y	14% (5)	--
	V170I	--	--

*Reference sequences for NS5A at amino acid 28 are M (genotype 1a) and L (genotype 1b).

†Reference sequences for NS5A at amino acid 31 are L (genotype 1a and genotype 1b).

‡Reference sequences for NS5A at amino acid 58 are H (genotype 1a) and P (genotype 1b).

In Vitro Cross Resistance

Elbasvir is active *in vitro* against genotype 1a NS5A substitutions, M28V and Q30L, genotype 1b substitutions, L28M/V, R30Q, L31V, Y93C, and genotype 4 substitution, M31V which confer resistance to other NS5A inhibitors. In general, other NS5A substitutions conferring resistance to NS5A inhibitors may also confer resistance to elbasvir. NS5A substitutions conferring resistance to elbasvir may reduce the antiviral activity of other NS5A inhibitors. Elbasvir is fully active against substitutions conferring resistance to NS3/4A protease inhibitors.

Grazoprevir is active *in vitro* against the following genotype 1a NS3 substitutions which confer resistance to other NS3/4A protease inhibitors: V36A/L/M, Q41R, F43L, T54A/S, V55A/I, Y56F, Q80K/R, V107I, S122A/G/R/T, I132V, R155K, A156S, D168N/S, I170T/V. Grazoprevir is active *in vitro* against the following genotype 1b NS3 substitutions conferring resistance to other NS3/4A protease inhibitors: V36A/I/L/M, Q41L/R, F43S, T54A/C/G/S, V55A/I, Y56F, Q80L/R, V107I, S122A/G/R, R155E/K/N/Q/S, A156G/S, D168E/N/S, V170A/I/T. Some NS3 substitutions at A156 and at D168 confer reduced antiviral activity to grazoprevir as well as to other NS3/4A protease inhibitors. Grazoprevir is fully active against resistance-associated variants selected by NS5A inhibitors.

The substitutions associated with resistance to NS5B inhibitors are susceptible to elbasvir or grazoprevir.

Persistence of Resistance-Associated Substitutions

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

Treatment-emergent NS5A resistance-associated substitutions were generally more persistent than NS3 resistance-associated substitutions. Among genotype 1-infected subjects who had one or more treatment-emergent NS5A resistance-associated substitutions, these substitutions became undetectable at follow-up week 12 in only 5% (2/44) of subjects and 0% (0/12) of subjects with follow-up week 24 data.

Among genotype 1-infected subjects with treatment-emergent NS3 resistance-associated substitutions, these substitutions became undetectable at follow-up week 24 in 67% (10/15) of subjects based on population sequencing.

Effect of Baseline HCV Polymorphisms on Treatment Response

Analyses in Phase 2 and 3 clinical studies of ZEPATIER, or elbasvir + grazoprevir, with or without ribavirin were conducted to explore the association between baseline NS5A and/or NS3 polymorphisms and treatment response among subjects who achieved SVR or experienced virologic failure *[see 9 CLINICAL STUDIES, 9.1 Overview of Clinical Trials]* and for whom baseline sequences were available. Baseline NS5A polymorphism at position 28, 30, 31, 58, and 93 were evaluated. Compared to a reference HCV genotype 1a replicon, the following NS5A substitutions reduced elbasvir antiviral activity by greater than 5-fold: M28T/A,

Q30E/H/R/G/K/D, L31M/V/F, H58D, and Y93C/H/N. Baseline NS3 polymorphisms at position 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175 were evaluated.

Genotype 1a

In pooled analyses of genotype 1a-infected subjects, baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro* were identified in 6% (29/491) of treatment-naïve subjects and 8% (26/334) of treatment-experienced subjects. Among treatment-naïve subjects, SVR was achieved in 98% (432/439) of subjects without baseline NS5A polymorphisms and 55% (16/29) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.* Among treatment-experienced subjects, SVR was achieved in 99% (291/295) of subjects without baseline NS5A polymorphisms and 50% (13/26) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.*

In pooled analyses, presence of NS3 polymorphisms, including Q80K, prior to the start of therapy did not impact treatment response among genotype 1a-infected subjects.

Genotype 1b

In pooled analyses, presence of NS5A polymorphisms prior to the start of therapy did not impact treatment response among treatment-naïve genotype 1b-infected subjects. NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro* were detected in 14% (36/259) of treatment-experienced subjects. SVR was achieved in 100% (223/223) of subjects without baseline NS5A polymorphisms and 86% (31/36) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.*

In pooled analyses, presence of NS3 polymorphisms prior to the start of therapy did not impact treatment response among genotype 1b-infected subjects.

10.4 Pharmacokinetics

General Introduction

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 or sofosbuvir 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. Based on the population pharmacokinetic modeling in non-cirrhotic, HCV-infected subjects, the geometric mean steady-state elbasvir AUC_{0-24} and C_{max} at 50 mg were 2180 nM•hr and 137 nM, respectively, and the geometric mean steady-state grazoprevir AUC_{0-24} and C_{max} at 100 mg were 1860 nM•hr and 220 nM, respectively. Following once daily administration of ZEPATIER to HCV-infected subjects, elbasvir and grazoprevir reached steady state within approximately 6 days.

Absorption

Absorption

Following administration of ZEPATIER to HCV-infected subjects, elbasvir peak plasma concentrations occur at a median T_{max} of 3 hours (range of 3 to 6 hours); grazoprevir peak plasma concentrations occur at a median T_{max} of 2 hours (range of 30 minutes to 3 hours). The absolute bioavailability of elbasvir is estimated to be 32% and grazoprevir is estimated to be 10 to 40%.

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.

Distribution

Elbasvir and grazoprevir are extensively bound (>99.9% and 98.8%, respectively) to human plasma proteins. Both elbasvir and grazoprevir bind to human serum albumin and α1-acid glycoprotein. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

In preclinical distribution studies, elbasvir distributes into most tissues including the liver; whereas grazoprevir distributes predominantly to the liver likely facilitated by active transport through the OATP1B liver uptake transporter.

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.

Elimination

The geometric mean apparent terminal half-life (% geometric mean coefficient of variation) is approximately 24 (24%) hours at 50 mg elbasvir and approximately 31 (34%) hours at 100 mg grazoprevir in HCV-infected subjects.

Excretion

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

Special Populations

Renal Impairment

The pharmacokinetics of elbasvir and grazoprevir were evaluated in non-HCV-infected subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2) with or without hemodialysis and also in HCV-infected subjects with severe renal impairment with or without hemodialysis.

Relative to non-HCV-infected subjects with normal renal function (eGFR >80 mL/min/1.73 m^2), elbasvir and grazoprevir AUC values were increased by 86% and 65%, respectively, in non-HCV-infected subjects with severe renal impairment who were not on dialysis. Relative to subjects with normal renal function, elbasvir and grazoprevir AUC values were unchanged in non-HCV-infected subjects with dialysis-dependent, severe renal impairment. Elbasvir and grazoprevir are highly bound to plasma protein. Elbasvir and grazoprevir are not removed by hemodialysis. Concentrations of elbasvir were not quantifiable in the dialysate samples. Less than 0.5% of grazoprevir was recovered in dialysate over a 4-hour dialysis session. Elbasvir and grazoprevir are not expected to be removed by peritoneal dialysis.

In population pharmacokinetic analysis, elbasvir AUC was 25% higher in dialysis-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 dialysis-dependent subjects and 40% higher in non-dialysis-dependent subjects with severe renal impairment compared to grazoprevir AUC in subjects without severe renal impairment.

Overall, changes in exposure of elbasvir and grazoprevir in HCV-infected subjects with renal impairment with or without dialysis are not clinically relevant. Therefore, no dosage adjustment of ZEPATIER is recommended in HCV-infected subjects with renal impairment regardless of dialysis status *[see 6 USE IN SPECIFIC POPULATIONS, 6.8 Renal Impairment]*.

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 with mild hepatic impairment (CP-A) or moderate hepatic impairment (CP-B).

Elbasvir $AUC_{0\text{-}inf}$ was decreased by 40% in non-HCV-infected subjects with mild hepatic impairment (CP-A) compared to matching healthy subjects. In non-HCV-infected subjects with mild hepatic impairment, grazoprevir steady-state $AUC_{0\text{-}24}$ was increased 70% compared to matching healthy subjects. Population PK analyses of HCV-infected subjects in Phase 2 and 3 studies demonstrated that elbasvir steady-state AUC was similar in HCV-infected subjects with mild hepatic impairment compared to subjects without hepatic impairment. Grazoprevir steady-state $AUC_{0\text{-}24}$ increased by approximately 65% in HCV-infected subjects with compensated cirrhosis compared to HCV-infected, non-cirrhotic subjects. Based on these data, no dosage adjustment of ZEPATIER is recommended in HCV-infected subjects with mild hepatic impairment (CP-A), including those with compensated cirrhosis.

Elbasvir AUC decreased by 28% in non-HCV-infected subjects with moderate hepatic impairment (CP-B) compared to matched healthy subjects. Elbasvir steady-state AUC was similar in HCV-infected subjects with moderate hepatic impairment compared to subjects without hepatic impairment. Compared to healthy matched subjects, grazoprevir steady-state $AUC_{0\text{-}24}$ was increased 5-fold in non-HCV-infected subjects with moderate hepatic impairment. ZEPATIER is contraindicated in HCV-infected subjects with moderate hepatic impairment (CP-B) due to lack of clinical safety and efficacy experience in this population and the expected increase in grazoprevir exposure.

Elbasvir $AUC_{0\text{-}inf}$ is decreased by 12% in non-HCV-infected subjects with severe hepatic impairment (CP-C) compared to matching healthy subjects. Grazoprevir steady-state $AUC_{0\text{-}24}$ was increased 12-fold in non-HCV-infected subjects with severe hepatic impairment compared to healthy matched subjects. ZEPATIER is contraindicated in HCV-infected subjects with severe hepatic impairment (CP-C) based on the significant increase in grazoprevir exposure

observed in non-HCV-infected subjects with severe hepatic impairment *[see 3 CONTRAINDICATIONS and 6 USE IN SPECIFIC POPULATIONS, 6.9 Hepatic Impairment]*.

Pediatric

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

Geriatric

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 16% and 45% higher, respectively, in subjects ≥65 years of age compared to subjects less than 65 years of age. No dose adjustment of ZEPATIER is recommended based on age *[see 6 USE IN SPECIFIC POPULATIONS, 6.5 Geriatric Use]*.

Race

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 15% and 50% higher, respectively, for Asians compared to Whites. Population pharmacokinetics estimates of exposure of elbasvir and grazoprevir were comparable between Whites and Black/African Americans. No dose adjustment of ZEPATIER is recommended based on race/ethnicity.

Gender

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 50% and 30% higher, respectively, in females compared to males. No dose adjustment of ZEPATIER is recommended based on sex.

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. Therefore, no dose adjustment of ZEPATIER is recommended based on weight/BMI.

10.5 Drug Interaction Studies

Drug Interaction Studies

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 11 summarizes the effects of co-administered drugs on the exposures of the individual components of ZEPATIER

(elbasvir and grazoprevir). Table 12 summarizes the effects of the individual components of ZEPATIER on the exposures of the co-administered drugs. For information regarding clinical recommendations, *see 4 WARNINGS AND PRECAUTIONS, 4.4 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS.*

Elbasvir and grazoprevir are substrates of CYP3A/P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir is minimal. Co-administration of moderate and strong CYP3A/P-gp inducers with ZEPATIER may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration of strong CYP3A inhibitors with ZEPATIER may increase elbasvir and grazoprevir plasma concentrations *[see Table 2]*.

Grazoprevir is a substrate of OATP1B. Co-administration of ZEPATIER with drugs that inhibit OATP1B 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 Table 2 and 12]*.

Clinically significant drug interactions with ZEPATIER as an inhibitor of other CYP enzymes, UGT1A1, esterases (CES1, CES2, and CatA), organic anion transporters (OAT)1 and OAT3, and organic cation transporter (OCT)2 are not expected, and multiple-dose administration of elbasvir or grazoprevir is unlikely to induce the metabolism of drugs metabolized by CYP isoforms based on *in vitro* data. A clinical interaction study with montelukast confirmed that grazoprevir is not a CYP2C8 inhibitor (CYP isoform with lowest *in vitro* IC_{50}).

Elbasvir has minimal intestinal P-gp inhibition in humans, and does not result in clinically relevant increases in concentrations of digoxin (a P-gp substrate), with an 11% increase in plasma AUC *[see Table 12]*. Grazoprevir is not a P-gp inhibitor *in vitro*. Therefore, P-gp substrates may be administered without dose adjustment when co-administered with ZEPATIER.

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. Neither elbasvir nor grazoprevir are inhibitors of OATP1B in humans *[see 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS]*.

Table 11: 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)	--
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)
HIV Fixed-Dose Combination Regimen							
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	150 mg/ 150 mg/ 200 mg/ 300 mg once daily	EBR 50 mg / GZR 100 mg once daily	21	EBR	2.18 (2.02, 2.35)	1.91 (1.77, 2.05)	2.38 (2.19, 2.60)
		EBR 50 mg / GZR 100 mg once daily	21	GZR	5.36 (4.48, 6.43)	4.59 (3.70, 5.69)	2.78 (2.48, 3.11)
Immunosuppressant							
Cyclosporine	400 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.98 (1.84, 2.13)	1.95 (1.84, 2.07)	2.21 (1.98, 2.47)
	400 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	15.21 (12.83, 18.04)	17.00 (12.94, 22.34)	3.39 (2.82, 4.09)

Mycophenolate mofetil	1000 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.07 (1.00, 1.14)	1.07 (0.98, 1.16)	1.05 (0.97, 1.14)
	1000 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	0.74 (0.60, 0.92)	0.58 (0.42, 0.82)	0.97 (0.89, 1.06)
Prednisone	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.17 (1.11, 1.24)	1.25 (1.16, 1.35)	1.04 (0.97, 1.12)
	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	1.09 (0.95, 1.25)	1.34 (1.10, 1.62)	0.93 (0.87, 1.00)
Tacrolimus	2 mg single-dose	EBR 50 mg + GZR 200 mg once daily	16	EBR	0.97 (0.90, 1.06)	0.99 (0.88, 1.10)	0.92 (0.83, 1.02)
	2 mg single-dose	EBR 50 mg + GZR 200 mg once daily	16	GZR	1.12 (0.97, 1.30)	1.07 (0.83, 1.37)	0.94 (0.87, 1.02)
Opioid-Substitution Therapy							
Buprenorphine/naloxone	8 mg/2 mg single-dose	EBR 50 mg single-dose	15	EBR	1.22 (0.98, 1.52)	1.13 (0.87, 1.46)	1.22 (0.99, 1.51)
	8-24 mg/ 2-6 mg once daily	GZR 200 mg once daily	12	GZR	0.80 (0.53, 1.22)	0.76 (0.40, 1.44)	0.69 (0.54, 0.88)
Methadone	20-120 mg once daily	EBR 50 mg once daily	10	EBR	1.71 (1.16, 2.51)	1.93 (1.30, 2.86)	1.86 (1.22, 2.83)
	20-150 mg once daily	GZR 200 mg once daily	12	GZR	1.03 (0.53, 1.97)	0.88 (0.36, 2.14)	0.77 (0.56, 1.04)
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 12: 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/	EBR	50 mg once daily	9	1.02 (0.93, 1.13)	1.02 (0.92, 1.13)	1.07 (0.97, 1.18)

	ritonavir 100 mg twice 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 (1.08, 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)
	Tenofovir disoproxil	EBR/GZR	50 mg + 100 mg once daily	13	1.27 (1.20, 1.35)	1.14 (0.95, 1.36)	1.23 (1.09, 1.40)

	fumarate 300 mg once daily						
HIV Fixed-Dose Combination Regimen							
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	Elvitegravir 150 mg once daily	EBR/GZR	50 mg / 100 mg once daily	22	1.10 (1.00, 1.21)	1.02 (0.93, 1.11)	1.31 (1.11, 1.55)
	Cobicistat 150 mg once daily	EBR/GZR	50 mg / 100 mg once daily	22	1.49 (1.42, 1.57)	1.39 (1.29, 1.50)	--
	Emtricitabine 200 mg once daily	EBR/GZR	50 mg / 100 mg once daily	22	1.07 (1.03, 1.10)	0.96 (0.90, 1.02)	1.19 (1.13, 1.25)
	Tenofovir disoproxil fumarate 300 mg once daily	EBR/GZR	50 mg / 100 mg once daily	22	1.18 (1.13, 1.24)	1.25 (1.14, 1.37)	1.20 (1.15, 1.26)
Immunosuppressant							
Cyclosporine	Cyclosporine 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 20-150 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)
		GZR	200 mg once daily	12	1.09 (1.02, 1.17)	1.03 (0.96, 1.11)	--
S-Methadone		EBR	50 mg once daily	10	1.09 (0.94, 1.26)	1.09 (0.95, 1.25)	1.20 (0.98, 1.47)
		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)
	Atorvastatin 20 mg single-dose	GZR	200 mg once daily	9	3.00 (2.42, 3.72)	5.66 (3.39, 9.45)	--
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)
		GZR	200 mg once daily	12	1.59 (1.33, 1.89)#	4.25 (3.25, 5.56)	0.80 (0.70, 0.91)

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

*$AUC_{0\text{-}inf}$ 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

11. ANIMAL TOXICOLOGY

11.1 General Toxicology

Elbasvir

No adverse target organ toxicity was identified. The No-Observed Adverse Effect Levels (NOAEL) in rats, dogs, and in rasH2 wild-type mice was the highest dose tested, 1000 mg/kg/day (exposure approximately 9-, 7-, and 63-fold, respectively higher than exposure in humans at the recommended clinical dose).

Grazoprevir

The target organs identified in the repeat-dose toxicity studies were the hepatobiliary system (mouse, rat, and dog), the male reproductive organs (mouse and dog), the gastrointestinal tract (mouse, rat, and dog), the kidney (mouse only), and the spleen/bone marrow (dog only). The changes in these organs were considered of limited toxicological significance based on their nature (i.e., when not associated with any evidence of inflammation, or degeneration/necrosis) or severity, and/or not relevant at the human exposure based on high safety multiples (>50-fold margins).

The NOAELs in rats and dogs were 200 mg/kg b.i.d., i.e., 400 mg/kg/day – highest dose tested - (exposure approximately 226-fold higher than exposure in humans at the recommended clinical dose) and 15 mg/kg/day (approximately 186-fold higher than exposure in humans at the recommended clinical dose), respectively. The NOAELs in rasH2 wild-type mice and CD1 mice were 100 mg/kg/day (exposure approximately 83X higher than exposure in humans at the recommended clinical dose) and 200 mg/kg/day (exposure approximately 416X higher than exposure in humans at the recommended clinical dose), respectively.

11.2 Carcinogenesis

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 also applies to this combination regimen *[see prescribing information for ribavirin]*.

11.3 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.

If ZEPATIER is administered in a regimen containing ribavirin, the information for ribavirin on carcinogenesis also applies to this combination regimen *[see prescribing information for ribavirin]*.

11.4 Reproduction

Fertility

No human data on the effect of elbasvir or grazoprevir on fertility are available. No effects on mating, female or male fertility, or early embryonic development were observed in rats up to the highest dose tested. AUC exposure to elbasvir and grazoprevir was approximately 7- and 108-fold, respectively, the exposure in humans at the recommended clinical dose.

If ZEPATIER is administered in a regimen containing ribavirin, the information for ribavirin on carcinogenesis also applies to this combination regimen *[see prescribing information for ribavirin]*.

11.5 Development

Elbasvir:

No effects on embryo-fetal development or maternal toxicity have been observed in rats or rabbits when dams were administered elbasvir up to the highest dose tested during early embryonic development (rats), organogenesis (rats and rabbits), or perinatal period (rats). In the rat and rabbit, AUC exposure to elbasvir was approximately 9- and 17-fold, respectively, the exposure in humans at the recommended clinical dose. In both species, elbasvir has been shown to cross the placenta.

No effects on postnatal development in nursing rats and no maternal toxicity have been observed when lactating dams were administered elbasvir up to the highest dose tested. AUC

exposure to elbasvir was approximately 9-fold the exposure in humans at the recommended clinical dose. Elbasvir has been shown to be excreted into the milk of lactating rats. Elbasvir was excreted into the milk of lactating rats with concentrations 4-fold that of the maternal plasma concentrations.

Grazoprevir:
No effects on embryo-fetal development or maternal toxicity have been observed in rats or rabbits when dams were administered grazoprevir up to the highest dose tested during early embryonic development (rats), organogenesis (rats and rabbits), or perinatal period (rats). In the rat and rabbit, AUC exposure to grazoprevir was approximately 79- and 39-fold, respectively, the exposure in humans at the recommended clinical dose. In both species, grazoprevir has been shown to cross the placenta.

No effects on postnatal development in nursing rats and no maternal toxicity have been observed when lactating dams were administered grazoprevir up to the highest dose tested. AUC exposure to grazoprevir was approximately 79-fold the exposure in humans at the recommended clinical dose. Grazoprevir has been shown to be excreted into the milk of lactating rats. Grazoprevir was excreted into the milk of lactating rats with concentrations <1-fold of the maternal plasma concentrations.

12. NAME OF THE DRUG

ZEPATIER

13. PHARMACEUTICAL FORM

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

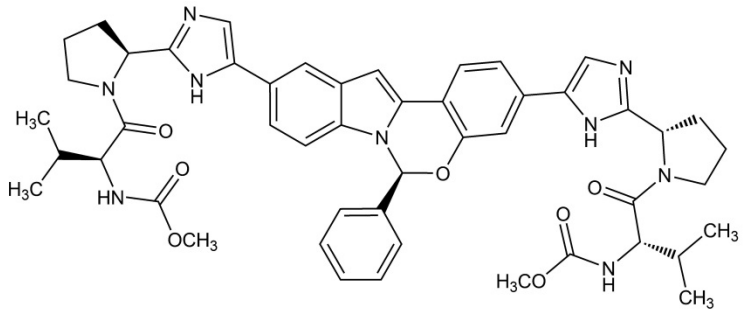
14. PHARMACEUTICAL PARTICULARS

14.1 Chemistry

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:

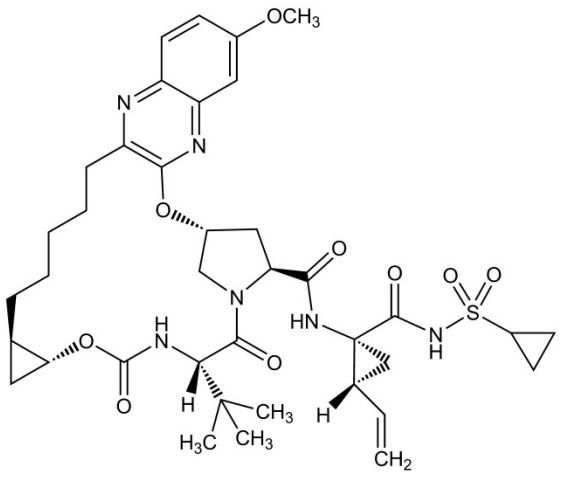


Elbasvir is practically insoluble in water (<0.1 mg/mL) and very slightly soluble in ethanol (0.2 mg/mL), but is very soluble in ethyl acetate and acetone.

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 (<0.1 mg/mL) but is freely soluble in ethanol and some organic solvents (e.g., acetone, tetrahydrofuran and N,N-dimethylformamide).

14.2 Composition

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.

Active Ingredient

Each tablet contains 50 mg elbasvir and 100 mg grazoprevir.

Inactive Ingredients (List of excipients)

The tablets include the following inactive ingredients: sodium lauryl sulfate, vitamin E polyethylene glycol succinate, copovidone, hypromellose, microcrystalline cellulose, mannitol, lactose monohydrate, croscarmellose sodium, sodium chloride, colloidal silicon dioxide, and magnesium stearate. The tablets are film-coated with a coating material containing the following inactive ingredients: lactose monohydrate, hypromellose, titanium dioxide, triacetin, iron oxide yellow, iron oxide red, ferrosoferric oxide, and carnauba wax.

14.3 Storage

Special Precautions for Storage

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

Store below 30°C

14.4 Shelf Life

36 months

14.5 Availability (a.k.a. Nature and Contents of Container)

Reg. No.: DKI1787102417A1
Box, 2 envelopes @ 2 blisters @ 7 film coated tablets

14.6 Special Precautions for Disposal and Other Handling

On Medical Prescription Only
HARUS DENGAN RESEP DOKTER

Manufactured by : MSD International GmbH, Ireland

Released by : Schering-Plough Labo N.V., Belgium

Registered by :

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

Distributed by :

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

S-CCDS-MK5172A-T-022016

S-CCDS-MK5172A-T-092016

S-CCDS-MK5172A-T-032017

S-CCDS-MK5172A-T-022020 ver 2.0

MSD

DISETUJUI OLEH BPOM : 08/06/2021 ID : EREG100373VR12100077

ZEPATIER (elbasvir and grazoprevir)
Tablet Salut Selaput

Harap membaca leaflet ini dengan seksama sebelum Anda mulai minum obat, walaupun Anda telah menggunakan obat ini sebelumnya. Beberapa informasi dalam leaflet sebelumnya dapat berubah.

Ingatlah bahwa dokter Anda meresepkan obat ini hanya untuk Anda. Jangan berikan kepada orang lain.

Dokter Anda mungkin memberikan ZEPATIER dengan ribavirin. Penting bagi Anda untuk membaca informasi produk untuk obat-obat lain tersebut jika Anda mengkonsumsinya bersama dengan Zepatier.

Jika Anda mempunyai pertanyaan tentang obat Anda, silahkan bertanya kepada dokter Anda atau apoteker.

1.APAKAH ZEPATIER ?

ZEPATIER (elbasvir dan grazoprevir) merupakan tablet salut selaput. ZEPATIER mengandung bahan aktif 50 mg elbasvir dan 100 mg grazoprevir.

Sebagai tambahan, ZEPATIER juga mengandung bahan inaktif seperti : sodium lauryl sulfate, vitamin E polyethylene glycol succinate, copovidone, hypromellose, microcrystalline cellulose, mannitol, lactose monohydrate, croscarmellose sodium, sodium chloride, colloidal silicon dioxide, dan magnesium stearate. Tablet merupakan salut selaput dengan bahan penyalut yang mengandung bahan inaktif seperti : lactose monohydrate, hypromellose, titanium dioxide, triacetin, iron oxide yellow, iron oxide red, ferrosoferric oxide, dan carnauba wax.

Zepatier merupakan obat antivirus yang bekerja secara langsung untuk terapi infeksi Hepatitis C genotip 1a dan 1b.

Hepatitis C merupakan virus yang menginfeksi hati. Zat aktif yang terdapat di dalam obat tersebut bekerja bersama-sama dengan cara memblok 2 protein yang berbeda yang diperlukan virus

hepatitis C untuk memperbanyak virus.

2.MENGAPA DOKTER SAYA MERESEPKAN ZEPATIER ?

ZEPATIER diindikasikan pada orang dewasa untuk pengobatan infeksi hepatitis C yang kronis (*long-lasting*).

3.BAGAIMANA CARA MENGGUNAKAN ZEPATIER ?

Minumlah ZEPATIER sesuai anjuran dokter kepada Anda.

- **Minumlah satu tablet per hari pada jam yang sama setiap hari.**
- ZEPATIER dikemas dalam blister yang berisi tablet.
  Simpanlah tablet di dalam kemasan sampai Anda siap untuk meminum obat.
- Anda dapat meminum zepatier dengan atau tanpa makanan.
- Jangan berhenti minum Zepatier sebelum membicarakan terlebih dahulu dengan dokter Anda.

3.1 Apa yang harus saya lakukan bila terjadi overdosis ?

Jika Anda meminum melebihi dosis yang diberikan , segera hubungi dokter Anda.

3.2 Apa yang harus saya lakukan bila saya lupa minum satu dosis ?

Penting sekali untuk Anda tidak lupa meminum obat ini. Jika Anda lupa minum satu dosis, segera mengingat berapa lama sejak Anda terakhir meminum Zepatier:

- Bila kurang dari 16 jam sejak dari dosis terakhir yang Anda minum, maka minum obat tersebut secepatnya. Kemudian minum dosis berikutnya sesuai jadwal minum obat seperti biasanya.

- Bila lebih dari 16 jam sejak dari dosis terakhir yang Anda minum, jangan meminum dosis obat yang terlupakan. Tunggu dan minum dosis selanjutnya sesuai jadwal minum obat Anda.

- Jangan meminum obat dengan dosis ganda (dua tablet bersamaan) untuk mencukupi dosis yang terlupakan sebelumnya.

4.APAKAH YANG HARUS SAYA KETAHUI SEBELUM MENGGUNAKAN ZEPATIER ?

4.1Siapa yang tidak boleh menggunakan ZEPATIER ?

Jangan meminum ZEPATIER jika Anda :

- alergi terhadap elbasvir, grazoprevir atau kandungan lainnya dari ZEPATIER.
  Lihat bagian " 1. APAKAH ZEPATIER?" pada informasi produk pasien untuk mendapatkan daftar lengkap dari kandungan ZEPATIER.
- Mempunyai gangguan fungsi hati sedang hingga berat
- Anda sedang meminum obat-obatan dibawah ini:
  - nafcillin
  - cyclosporine
  - Terapi HIV termasuk: efavirenz, etravirine, atazanavir, darunavir, lopinavir, saquinavir, atau tipranavir
  - phenytoin
  - carbamazepine
  - rifampin
  - bosentan
  - St. John's wort (Hypericum perforatum)
  - modafinil

4.2 Apa yang harus saya informasikan kepada dokter saya sebelum menggunakan ZEPATIER ?

Informasikan kepada dokter Anda jika Anda :

- pernah menderita hepatitis B
- pernah meminum obat untuk hepatitis C
- mempunyai gangguan hati lainnya selain hepatitis C
- sudah, atau sedang menunggu transplantasi hati
- mempunyai kondisi medis yang lain
- sedang hamil, sedang berencana untuk hamil , menyusui atau berencana untuk menyusui

Dokter Anda akan memutuskan apakah ZEPATIER adalah obat yang tepat untuk Anda.

Anda juga bisa mendapatkan informasi dari dokter Anda atau apoteker, yang mempunyai

informasi yang lebih detail.

4.3 Hamil

- Informasikan dokter Anda jika Anda sedang hamil atau berencana untuk hamil.
- Kami tidak tahu apakah ZEPATIER akan memberikan dampak yang merugikan untuk bayi Anda ketika Anda sedang hamil.

Jika Anda meminum ZEPATIER dan ribavirin

- **Jika Anda atau pasangan Anda sedang hamil atau berencana untuk hamil, jangan meminum ribavirin**. Hindari kehamilan dalam waktu 6 bulan sejak ribavirin dihentikan.

  Bacalah leaflet ribavirin untuk informasi penting terkait kehamilan dan kontrasepsi.
- Jika Anda (atau pasangan Anda) sedang hamil saat meminum ribavirin atau dalam waktu 6 bulan setelah Anda berhenti meminum ribavirin, segera beritahu dokter Anda.

4.4 Menyusui

- Informasikan dokter Anda jika Anda sedang menyusui atau berencana untuk menyusui.
- Kami tidak tahu apakah ZEPATIER dapat terkandung didalam asi (air susu ibu) Anda dan diteruskan ke bayi Anda.
- Bacalah leaflet ribavirin untuk informasi penting terkait menyusui.

Dokter Anda akan memutuskan apakah ZEPATIER adalah obat yang tepat untuk Anda.

4.5 Anak-anak

Belum diketahui apakah ZEPATIER aman atau efektif untuk anak-anak dibawah 18 tahun.

4.6 Dapatkah saya meminum ZEPATIER dengan obat lain,suplemen makanan,produk herbal atau makanan ?

Informasikan kepada dokter Anda tentang semua obat-obatan yang Anda minum, termasuk obat-obatan resep dan non-resep, vitamin, dan suplemen herbal. ZEPATIER dapat mempengaruhi cara kerja obat-obatan lain, dan obat-obatan lainnya dapat mempengaruhi cara kerja ZEPATIER. Obat-obatan yang harus diinformasikan kepada dokter Anda meliputi:

- obat yang tidak boleh digunakan bersama Zepatier seperti pada point 4.1
- kombinasi terapi HIV yang mengandung cobicistat, elvitegravir, emtricitabine, and tenofovir
- oral ketoconazole
- sunitinib
- tacrolimus
- statin tertentu (atorvastatin, fluvastatin, lovastatin, rosuvastatin, atau simvastatin)
- dabigatran etexilate
- warfarin dan obat serupa lainnya yang disebut antagonis vitamin K
- Obat-obatan untuk mengobati diabetes

Lihat juga "4.1Siapa yang tidak boleh menggunakan ZEPATIER ?"

Ketahuilah obat-obatan yang Anda minum. Simpanlah daftar obat Anda dan tunjukkan kepada dokter dan apoteker ketika Anda mendapatkan obat baru.

Jika salah satu di atas berlaku pada Anda (atau Anda tidak yakin), diskusikan dengan dokter Anda atau apoteker sebelum meminum ZEPATIER.

5.APAKAH EFEK YANG TIDAK DIINGINKAN YANG DIMILIKI OLEH ZEPATIER ?

Obat apapun mempunyai efek yang tidak diinginkan, yang disebut sebagai efek samping.

Reaktivasi virus Hepatitis B: Sebelum memulai pengobatan dengan ZEPATIER, penyedia layanan kesehatan Anda akan melakukan tes darah untuk memeriksa infeksi virus hepatitis B. Jika Anda pernah mengalami infeksi virus hepatitis B, virus hepatitis B dapat menjadi aktif kembali selama atau setelah pengobatan infeksi virus hepatitis C dengan ZEPATIER. Virus Hepatitis B menjadi aktif kembali (disebut reaktivasi) dapat menyebabkan masalah hati yang serius termasuk gagal hati dan kematian. Penyedia layanan kesehatan Anda akan memantau Anda jika Anda memiliki risiko reaktivasi virus hepatitis B selama perawatan dan setelah Anda berhenti minum ZEPATIER.

Efek samping yang sangat umum terjadi : dapat terjadi lebih dari 1 dari 10 orang

- sakit kepala
- merasa sangat lelah (kelelahan)

Efek samping yang umum terjadi : dapat terjadi hingga 1 dari 10 orang

- mual
- merasa mudah tersinggung

- merasa lemah atau kekurangan energi (asthenia)
- gatal
- diare
- kesulitan untuk tidur (insomnia)
- nyeri sendi atau nyeri, bengkak sendi
- susah buang air besar
- merasa pusing
- kehilangan selera makan
- sakit otot
- sakit perut
- rambut rontok yang tidak biasa atau menipis
- merasa gugup
- depresi
- mulut kering
- muntah

Efek samping yang tidak umum terjadi : dapat terjadi hingga 1 dari 10 orang

- kelainan pada hasil tes laboratorium fungsi hati

Jika Anda memiliki efek samping yang mengganggu Anda atau yang tidak hilang, beritahu dokter Anda.

Mungkin ada efek samping lain untuk ZEPATIER yang tidak terdaftar. Untuk informasi lebih lanjut atau saran medis hubungi dokter Anda.

6.BERAPA LAMA SAYA DAPAT MENYIMPAN OBAT SAYA ?

Simpan ZEPATIER sampai tanggal kadaluarsa sesuai yang tertera di karton.

7.BAGAIMANA SAYA MENYIMPAN ZEPATIER ?

Simpan ZEPATIER dibawah suhu 30^{o}C.

Simpan ZEPATIER di dalam kemasan blister aslinya sampai Anda siap untuk meminumnya. Jangan keluarkan tablet dari kemasan blister asli untuk di simpan ke dalam wadah lain seperti kotak tablet. Hal ini penting karena tablet sangat peka terhadap kelembaban. Kemasan blister dirancang untuk melindungi obat tersebut.

Jauhkan ZEPATIER dan obat-obatan lainnya dari jangkaun anak-anak.

8. BAGAIMANA SAYA DAPAT MENGETAHUI LEBIH TENTANG ZEPATIER DAN KONDISI SAYA ?

Anda dapat mengetahui informasi lebih lanjut dari dokter Anda dan apoteker.

Kemasan:

Reg. No.: DKI1787102417A1

Dus, 2 amplop @ 2 blister @ 7 tablet salut selaput

HARUS DENGAN RESEP DOKTER

Dibuat oleh: MSD International GmbH, Ireland

Diluluskan oleh : Schering-Plough Labo N.V., Belgium

Didaftarkan oleh:

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

Didistribusikan oleh:

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

S-CCPPI-MK5172A-T-022016

S-CCPPI-MK5172A-T-092016

S-CCPPI-MK5172A-T-032017

S-CCPPI-MK5172A-T-022020

DISETUJUI OLEH BPOM : 08/06/2021 ID : EREG100373VR12100077