SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

ZEPATIER® 50 mg/100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg elbasvir and 100 mg grazoprevir.

Excipients with known effect

Each film-coated tablet contains 87.02 mg of lactose (as monohydrate) and 69.85 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Beige, oval tablet of dimensions 21 mm x 10 mm debossed with “770” on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZEPATIER is indicated for the treatment of chronic hepatitis C (CHC) in adult and paediatric patients 12 years of age and older who weigh at least 30 kg (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype-specific activity see sections 4.4 and 5.1.

4.2 Posology and method of administration

ZEPATIER treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Posology

The recommended dose is one tablet once daily.

Recommended regimens and treatment durations are provided in Table 1 below (see sections 4.4 and 5.1):

Table 1: Recommended ZEPATIER therapy for treatment of chronic hepatitis C infection in patients with or without compensated cirrhosis (Child-Pugh A only)

HCV genotype	Treatment and duration
1a	ZEPATIER for 12 weeks ZEPATIER for 16 weeks plus ribavirin[A] should be considered in patients with baseline HCV RNA level >800,000 IU/mL and/or the presence of specific NS5A polymorphisms causing at least a 5-fold reduction in activity of elbasvir to minimise the risk of treatment failure (see section 5.1).
1b	ZEPATIER for 12 weeks
4	ZEPATIER for 12 weeks ZEPATIER for 16 weeks plus ribavirin[A] should be considered in patients with baseline HCV RNA level >800,000 IU/mL to minimise the risk of treatment failure (see section 5.1).

[A] In the adult clinical studies, the dose of ribavirin was weight-based (< 66 kg = 800 mg/day, 66 to 80 kg = 1,000 mg/day, 81 to 105 kg = 1,200 mg/day, > 105 kg = 1,400 mg/day) administered in two divided doses with food.

For specific dosage instructions for ribavirin, including dose modification, refer to the ribavirin Summary of Product Characteristics.

Patients should be instructed that if vomiting occurs within 4 hours of dosing, an additional tablet can be taken up to 8 hours before the next dose. If vomiting occurs more than 4 hours after dosing, no further dose is needed.

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.

Elderly
No dose adjustment of ZEPATIER is required for elderly patients (see sections 4.4 and 5.2).

Renal impairment and end stage renal disease (ESRD)
No dose adjustment of ZEPATIER is required in patients with mild, moderate, or severe renal impairment (including patients receiving haemodialysis or peritoneal dialysis) (see section 5.2).

Hepatic impairment
No dose adjustment of ZEPATIER is required in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (see sections 4.3 and 5.2).

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

Paediatric population
No dosage adjustment of ZEPATIER is required in paediatric patients 12 years of age and older who weigh at least 30 kg (see sections 5.1 and 5.2).
The safety and efficacy of ZEPATIER in children aged less than 12 years have not been established.

Method of administration

For oral use.

The film-coated tablets should be swallowed whole and may be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients with moderate or severe hepatic impairment (Child-Pugh B or C) (see sections 4.2 and 5.2).

Co-administration with inhibitors of organic anion transporting polypeptide 1B (OATP1B), such as rifampicin, atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cobicistat or ciclosporin (see sections 4.4 and 4.5).

Co-administration with inducers of cytochrome P450 3A (CYP3A) or P-glycoprotein (P-gp), such as efavirenz, phenytoin, carbamazepine, bosentan, etravirine, modafinil or St. John’s wort (*Hypericum perforatum*) (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

ALT elevations

The rate of late ALT elevations during treatment is directly related to the plasma exposure to grazoprevir. During clinical studies 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), (see section 4.8). 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 sections 4.8 and 5.2). These late ALT elevations generally occurred at or after treatment week 8.

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 discoloured faeces.
- Discontinuation of ZEPATIER should be considered if ALT levels are confirmed to be greater than 10 times the ULN.
- ZEPATIER should be discontinued if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

Genotype-specific activity

The efficacy of ZEPATIER has not been demonstrated in HCV genotypes 2, 3, 5 and 6. ZEPATIER is not recommended in patients infected with these genotypes.

Retreatment

The efficacy of ZEPATIER in patients previously exposed to ZEPATIER, or to medicinal products of the same classes as those of ZEPATIER (NS5A inhibitors or NS3/4A inhibitors other than telaprevir, simeprevir, boceprevir), has not been demonstrated (see section 5.1).

Interactions with medicinal products

Co-administration of ZEPATIER and OATP1B inhibitors is contraindicated because it may significantly increase grazoprevir plasma concentrations.

Co-administration of ZEPATIER and CYP3A or P-gp inducers is contraindicated because it may significantly decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced therapeutic effect of ZEPATIER (see sections 4.3, 4.5 and 5.2).

The concomitant use of ZEPATIER and strong CYP3A inhibitors increases elbasvir and grazoprevir concentrations, and co-administration is not recommended (see section 4.5).

HCV/HBV (hepatitis B virus) co-infection

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Use in diabetic patients

Diabetics may experience improved glucose control potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct acting antiviral (DAA) treatment. Glucose levels of diabetic patients initiating DAA therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when DAA therapy is initiated.

Paediatric population

ZEPATIER is not indicated for use in children under 12 years of age.

Excipients

ZEPATIER contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

ZEPATIER contains 69.85 mg sodium per tablet, equivalent to 3.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect ZEPATIER

Grazoprevir is a substrate of OATP1B drug transporters. Co-administration of ZEPATIER with medicinal products that inhibit OATP1B transporters is contraindicated because it may result in a significant increase in the plasma concentration of grazoprevir (see sections 4.3 and 4.4).

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 decrease elbasvir and grazoprevir plasma concentrations, which may lead to reduced therapeutic effect of ZEPATIER (see sections 4.3 and 4.4).

Co-administration of ZEPATIER with strong CYP3A inhibitors increases elbasvir and grazoprevir plasma concentrations, and co-administration is not recommended (see Table 2 and section 4.4). 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.

Potential for ZEPATIER to affect other medicinal products

Elbasvir and grazoprevir are inhibitors of the drug transporter 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 CYP3A inhibitor in humans. Co-administration with grazoprevir did not result in clinically relevant increases in exposures of CYP3A substrates. Therefore, no dose adjustment is required for CYP3A substrates when co-administered with ZEPATIER.

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. Grazoprevir is not a P-gp inhibitor based on *in vitro* data. Elbasvir and grazoprevir are not OATP1B inhibitors in humans. Based on *in vitro* data, clinically significant interactions with ZEPATIER as an inhibitor of other CYP enzymes, UGT1A1, esterases (CES1, CES2, and CatA), OAT1, OAT3, and OCT2 are not expected. Based on *in vitro* data, a potential for GZR to inhibit BSEP cannot be excluded. Multiple-dose administration of elbasvir or grazoprevir is unlikely to induce the metabolism of medicinal products metabolised by CYP isoforms based on in vitro data.

Patients treated with vitamin K antagonists

As liver function may change during treatment with ZEPATIER, a close monitoring of International Normalised Ratio (INR) values is recommended.

Impact of DAA therapy on drugs metabolized by the liver

Grazoprevir's weak inhibition of CYP3A may increase levels of CYP3A substrates. In addition, the plasma concentrations of drugs that are CYP3A substrates may be decreased by improvement in liver function during DAA therapy, related to clearance of HCV. Therefore, close monitoring and potential dose adjustment of CYP3A substrates with a narrow therapeutic index (e.g., calcineurin inhibitors) may be required during therapy, as drug levels may change (see Table 2).

Interactions between ZEPATIER and other medicinal products

Table 2 provides a listing of assessed or potential medicinal product 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 medicinal product interactions described are based on results from studies conducted with either ZEPATIER or elbasvir (EBR) and grazoprevir (GZR) as individual agents, or are predicted medicinal product interactions that may occur with elbasvir or grazoprevir. The table is not all-inclusive.

Table 2: Interactions and dose recommendations with other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (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 AUC 1.05 (0.92, 1.18) C_{max} 1.11 (0.98, 1.26) C_{24} 1.03 (0.91, 1.17) ↔ Grazoprevir AUC 1.10 (0.95, 1.28) C_{max} 0.89 (0.71, 1.11) C_{24} 1.12 (0.97, 1.30)	No dose adjustment is required.
Proton pump inhibitors		
Pantoprazole (40 mg once daily)/ elbasvir (50 mg single dose)/ grazoprevir (100 mg single dose)	↔ Elbasvir AUC 1.05 (0.93, 1.18) C_{max} 1.02 (0.92, 1.14) C_{24} 1.03 (0.92, 1.17) ↔ Grazoprevir AUC 1.12 (0.96, 1.30) C_{max} 1.10 (0.89, 1.37) C_{24} 1.17 (1.02, 1.34)	No dose adjustment is required.
Antacids		
Aluminium or magnesium hydroxide; calcium carbonate	Interaction not studied. Expected: ↔ Elbasvir ↔ Grazoprevir	No dose adjustment is required.
ANTIARRHYTHMICS		
Digoxin (0.25 mg single dose)/ elbasvir (50 mg once daily)	↔ Digoxin AUC 1.11 (1.02, 1.22) C_{max} 1.47 (1.25, 1.73) (P-gp inhibition)	No dose adjustment is required.
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.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
ANTIFUNGALS		
Ketoconazole		
(400 mg PO once daily)/ elbasvir (50 mg single dose)	↔ Elbasvir AUC 1.80 (1.41, 2.29) C_{max} 1.29 (1.00, 1.66) C_{24} 1.89 (1.37, 2.60)	Co-administration is not recommended.
(400 mg PO once daily)/ grazoprevir (100 mg single dose)	↑ Grazoprevir AUC 3.02 (2.42, 3.76) C_{max} 1.13 (0.77, 1.67) (CYP3A inhibition)	
ANTIMYCOBACTERIALS		
Rifampicin		
(600 mg IV single dose)/ elbasvir (50 mg single dose)	↔ Elbasvir AUC 1.22 (1.06, 1.40) C_{max} 1.41 (1.18, 1.68) C_{24} 1.31 (1.12, 1.53)	Co-administration is contraindicated.
(600 mg IV single dose)/ grazoprevir (200 mg single dose)	↑ Grazoprevir AUC 10.21 (8.68, 12.00) C_{max} 10.94 (8.92, 13.43) C_{24} 1.77 (1.40, 2.24) (OATP1B inhibition)	
(600 mg PO single dose)/ elbasvir (50 mg single dose)	↔ Elbasvir AUC 1.17 (0.98, 1.39) C_{max} 1.29 (1.06, 1.58) C_{24} 1.21 (1.03, 1.43)	
(600 mg PO single dose)/ grazoprevir (200 mg once daily)	↑ Grazoprevir AUC 8.35 (7.38, 9.45) C_{max} 6.52 (5.16, 8.24) C_{24} 1.31 (1.12, 1.53) (OATP1B inhibition)	
(600 mg PO once daily)/ grazoprevir (200 mg once daily)	↔ Grazoprevir AUC 0.93 (0.75, 1.17) C_{max} 1.16 (0.82, 1.65) C_{24} 0.10 (0.07, 0.13) (OATP1B inhibition and CYP3A induction)	
ASTHMA AGENTS		
Montelukast (10 mg single dose)/ grazoprevir (200 mg single dose)	↔ Montelukast AUC 1.11 (1.01, 1.20) C_{max} 0.92 (0.81, 1.06) C_{24} 1.39 (1.25, 1.56)	No dose adjustment is required.
ENDOTHELIN ANTAGONIST		
Bosentan	Interaction not studied. Expected: ↓ Elbasvir ↓ Grazoprevir (CYP3A or P-gp induction)	Co-administration is contraindicated.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg single dose sofosbuvir)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily	↔ Sofosbuvir AUC 2.43 (2.12, 2.79) C_{max} 2.27 (1.72, 2.99) ↔ GS-331007 AUC 1.13 (1.05, 1.21) C_{max} 0.87 (0.78, 0.96) C_{24} 1.53 (1.43, 1.63)	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 AUC 0.93 (0.82, 1.05) C_{max} 0.88 (0.77, 1.00) C_{24} 0.92 (0.18, 1.05) ↔ Tenofovir AUC 1.34 (1.23, 1.47) C_{max} 1.47 (1.32, 1.63) C_{24} 1.29 (1.18, 1.41)	No dose adjustment is required.
(300 mg once daily)/ grazoprevir (200 mg once daily)	↔ Grazoprevir AUC 0.86 (0.55, 1.12) C_{max} 0.78 (0.51, 1.18) C_{24} 0.89 (0.78, 1.01) ↔ Tenofovir AUC 1.18 (1.09, 1.28) C_{max} 1.14 (1.04, 1.25) C_{24} 1.24 (1.10, 1.39)	
(300 mg once daily)/elbasvir (50 mg once daily)/grazoprevir (100 mg once daily)	↔ Tenofovir AUC 1.27 (1.20, 1.35) C_{max} 1.14 (0.95, 1.36) C_{24} 1.23 (1.09, 1.40)	

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
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 AUC 1.07 (1.03, 1.10) C_{max} 0.96 (0.90, 1.02) C_{24} 1.19 (1.13, 1.25)	No dose adjustment is required.
HIV ANTIVIRAL AGENTS: PROTEASE INHIBITORS		
Atazanavir/ritonavir		
(300 mg once daily)/ ritonavir (100 mg once daily/ elbasvir (50 mg once daily)	↑ Elbasvir AUC 4.76 (4.07, 5.56) C_{max} 4.15 (3.46, 4.97) C_{24} 6.45 (5.51, 7.54) (combination of mechanisms including CYP3A inhibition) ↔ Atazanavir AUC 1.07 (0.98, 1.17) C_{max} 1.02 (0.96, 1.08) C_{24} 1.15 (1.02, 1.29)	Co-administration is contraindicated.
(300 mg once daily)/ ritonavir (100 mg once daily/ grazoprevir (200 mg once daily)	↑ Grazoprevir AUC 10.58 (7.78, 14.39) C_{max} 6.24 (4.42, 8.81) C_{24} 11.64 (7.96, 17.02) (combination of OATP1B and CYP3A inhibition) ↔ Atazanavir AUC 1.43 (1.30, 1.57) C_{max} 1.12 (1.01, 1.24) C_{24} 1.23 (1.13, 2.34)	

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (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 AUC 1.66 (1.35, 2.05) C_{max} 1.67 (1.36, 2.05) C_{24} 1.82 (1.39, 2.39) ↔ Darunavir AUC 0.95 (0.86, 1.06) C_{max} 0.95 (0.85, 1.05) C_{12} 0.94 (0.85, 1.05)	Co-administration is contraindicated.
(600 mg twice daily)/ ritonavir (100 mg twice daily/ grazoprevir (200 mg once daily)	↑ Grazoprevir AUC 7.50 (5.92, 9.51) C_{max} 5.27 (4.04, 6.86) C_{24} 8.05 (6.33, 10.24) (combination of OATP1B and CYP3A inhibition) ↔ Darunavir AUC 1.11 (0.99, 1.24) C_{max} 1.10 (0.96, 1.25) C_{12} 1.00 (0.85, 1.18)	
Lopinavir/ritonavir		
(400 mg twice daily)/ ritonavir (100 mg twice daily/ elbasvir (50 mg once daily)	↑ Elbasvir AUC 3.71 (3.05, 4.53) C_{max} 2.87 (2.29, 3.58) C_{24} 4.58 (3.72, 5.64) (combination of mechanisms including CYP3A inhibition) ↔ Lopinavir AUC 1.02 (0.93, 1.13) C_{max} 1.02 (0.92, 1.13) C_{12} 1.07 (0.97, 1.18)	Co-administration is contraindicated.
(400 mg twice daily)/ ritonavir (100 mg twice daily/ grazoprevir (200 mg once daily)	↑ Grazoprevir AUC 12.86 (10.25, 16.13) C_{max} 7.31 (5.65, 9.45) C_{24} 21.70 (12.99, 36.25) (combination of OATP1B and CYP3A inhibition) ↔ Lopinavir AUC 1.03 (0.96, 1.16) C_{max} 0.97 (0.88, 1.08) C_{12} 0.97 (0.81, 1.15)	
Saquinavir/ritonavir Tipranavir/ritonavir Atazanavir	Interaction not studied. *Expected:* ↑ Grazoprevir (combination of mechanisms including CYP3A inhibition)	Co-administration is contraindicated.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (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 AUC 0.46 (0.36, 0.59) C_{max} 0.55 (0.41, 0.73) C_{24} 0.41 (0.28, 0.59) (CYP3A or P-gp induction) ↔ Efavirenz AUC 0.82 (0.78, 0.86) C_{max} 0.74 (0.67, 0.82) C_{24} 0.91 (0.87, 0.96)	Co-administration is contraindicated.
(600 mg once daily)/ grazoprevir (200 mg once daily)	↓Grazoprevir AUC 0.17 (0.13, 0.24) C_{max} 0.13 (0.09, 0.19) C_{24} 0.31 (0.25, 0.38) (CYP3A or P-gp induction) ↔ Efavirenz AUC 1.00 (0.96, 1.05) C_{max} 1.03 (0.99, 1.08) C_{24} 0.93 (0.88, 0.98)	
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 AUC 1.07 (1.00, 1.15) C_{max} 1.07 (0.99, 1.16) C_{24} 1.04 (0.98, 1.11) ↔ Grazoprevir AUC 0.98 (0.89, 1.07) C_{max} 0.97 (0.83, 1.14) C_{24} 1.00 (0.93, 1.07) ↔ Rilpivirine AUC 1.13 (1.07, 1.20) C_{max} 1.07 (0.97, 1.17) C_{24} 1.16 (1.09, 1.23)	No dose adjustment is required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
HIV ANTIVIRAL AGENTS: INTEGRASE STRAND TRANSFER INHIBITORS		
Dolutegravir (50 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir AUC 0.98 (0.93, 1.04) C_{max} 0.97 (0.89, 1.05) C_{24} 0.98 (0.93, 1.03) ↔ Grazoprevir AUC 0.81 (0.67, 0.97) C_{max} 0.64 (0.44, 0.93) C_{24} 0.86 (0.79, 0.93) ↔ Dolutegravir AUC 1.16 (1.00, 1.34) C_{max} 1.22 (1.05, 1.40) C_{24} 1.14 (0.95, 1.36)	No dose adjustment is required.
Raltegravir		
(400 mg single dose)/ elbasvir (50 mg single dose)	↔ Elbasvir AUC 0.81 (0.57, 1.17) C_{max} 0.89 (0.61, 1.29) C_{24} 0.80 (0.55, 1.16) ↔ Raltegravir AUC 1.02 (0.81, 1.27) C_{max} 1.09 (0.83, 1.44) C_{12} 0.99 (0.80, 1.22)	No dose adjustment is required.
(400 mg twice daily)/ grazoprevir (200 mg once daily)	↔ Grazoprevir AUC 0.89 (0.72, 1.09) C_{max} 0.85 (0.62, 1.16) C_{24} 0.90 (0.82, 0.99) ↔ Raltegravir AUC 1.43 (0.89, 2.30) C_{max} 1.46 (0.78, 2.73) C_{12} 1.47 (1.08, 2.00)	

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
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 AUC 2.18 (2.02, 2.35) C_{max} 1.91 (1.77, 2.05) C_{24} 2.38 (2.19, 2.60) (CYP3A and OATP1B inhibition) ↑ Grazoprevir AUC 5.36 (4.48, 6.43) C_{max} 4.59 (3.70, 5.69) C_{24} 2.78 (2.48, 3.11) (CYP3A and OATP1B inhibition) ↔ Elvitegravir AUC 1.10 (1.00, 1.21) C_{max} 1.02 (0.93, 1.11) C_{24} 1.31 (1.11, 1.55) ↔ Cobicistat AUC 1.49 (1.42, 1.57) C_{max} 1.39 (1.29, 1.50) ↔ Emtricitabine AUC 1.07 (1.03, 1.10) C_{max} 0.96 (0.90, 1.02) C_{24} 1.19 (1.13, 1.25) ↔ Tenofovir AUC 1.18 (1.13, 1.24) C_{max} 1.25 (1.14, 1.37) C_{24} 1.20 (1.15, 1.26)	Co-administration with ZEPATIER is contraindicated.
HMG-CoA REDUCTASE INHIBITORS		
Atorvastatin		
(20 mg single dose)/ grazoprevir (200 mg once daily)	↑ Atorvastatin AUC 3.00 (2.42, 3.72) C_{max} 5.66 (3.39, 9.45) (primarily due to intestinal BCRP inhibition) ↔ Grazoprevir AUC 1.26 (0.97, 1.64) C_{max} 1.26 (0.83, 1.90) C_{24} 1.11 (1.00, 1.23)	The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER.
(10 mg single dose)/ elbasvir (50 mg once daily) / grazoprevir (200 mg once daily)	↑ Atorvastatin AUC 1.94 (1.63, 2.33) C_{max} 4.34 (3.10, 6.07) C_{24} 0.21 (0.17, 0.26)	

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
Rosuvastatin		
(10 mg single dose)/ grazoprevir (200 mg once daily)	↑ Rosuvastatin AUC 1.59 (1.33, 1.89) C_{max} 4.25 (3.25, 5.56) C24 0.80 (0.70, 0.91) (intestinal BCRP inhibition) ↔ Grazoprevir AUC 1.16 (0.94, 1.44) C_{max} 1.13 (0.77, 1.65) C_{24} 0.93 (0.84, 1.03)	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 AUC 2.26 (1.89, 2.69) C_{max} 5.49 (4.29, 7.04) C_{24} 0.98 (0.84, 1.13) (intestinal BCRP inhibition) ↔ Elbasvir AUC 1.09 (0.98, 1.21) C_{max} 1.11 (0.99, 1.26) C_{24} 0.96 (0.86, 1.08) ↔ Grazoprevir AUC 1.01 (0.79, 1.28) C_{max} 0.97 (0.63, 1.50) C_{24} 0.95 (0.87, 1.04)	
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 AUC 1.11 (0.91, 1.34) C_{max} 1.27 (1.07, 1.52) ↔ Grazoprevir AUC 0.81 (0.70, 0.95) C_{max} 0.72 (0.57, 0.92) C_{24} 0.91 (0.82, 1.01)	No dose adjustment is required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (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 AUC 1.33 (1.09, 1.64) C_{max} 1.28 (1.05, 1.55) ↔ Elbasvir AUC 0.98 (0.93, 1.02) C_{max} 0.97 (0.89, 1.05) C_{24} 0.97 (0.92, 1.02) ↔ Grazoprevir AUC 1.24 (1.00, 1.53) C_{max} 1.42 (1.00, 2.03) C_{24} 1.07 (0.99, 1.16)	No dose adjustment is required.
IMMUNOSUPPRESSANTS		
Ciclosporin (400 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir AUC 1.98 (1.84, 2.13) C_{max} 1.95 (1.84, 2.07) C_{24} 2.21 (1.98, 2.47) ↑ Grazoprevir AUC 15.21 (12.83, 18.04) C_{max} 17.00 (12.94, 22.34) C_{24} 3.39 (2.82, 4.09) (due in part to OATP1B and CYP3A inhibition) ↔ Ciclosporin AUC 0.96 (0.90, 1.02) C_{max} 0.90 (0.85, 0.97) C_{12} 1.00 (0.92, 1.08)	Co-administration is contraindicated.
Mycophenolate mofetil (1,000 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir AUC 1.07 (1.00, 1.14) C_{max} 1.07 (0.98, 1.16) C_{24} 1.05 (0.97, 1.14) ↔ Grazoprevir AUC 0.74 (0.60, 0.92) C_{max} 0.58 (0.42, 0.82) C_{24} 0.97 (0.89, 1.06) ↔ Mycophenolic acid AUC 0.95 (0.87, 1.03) C_{max} 0.85 (0.67, 1.07)	No dose adjustment is required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
Prednisone (40 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily	↔ Elbasvir AUC 1.17 (1.11, 1.24) C_{max} 1.25 (1.16, 1.35) C_{24} 1.04 (0.97, 1.12) ↔ Grazoprevir AUC 1.09 (0.95, 1.25) C_{max} 1.34 (1.10, 1.62) C_{24} 0.93 (0.87, 1.00) ↔ Prednisone AUC 1.08 (1.00, 1.17) C_{max} 1.05 (1.00, 1.10) ↔ Prednisolone AUC 1.08 (1.01, 1.16) C_{max} 1.04 (0.99, 1.09)	No dose adjustment is required.
Tacrolimus (2 mg single dose)/ elbasvir (50 mg once daily)/ grazoprevir (200 mg once daily)	↔ Elbasvir AUC 0.97 (0.90, 1.06) C_{max} 0.99 (0.88, 1.10) C_{24} 0.92 (0.83, 1.02) ↔ Grazoprevir AUC 1.12 (0.97, 1.30) C_{max} 1.07 (0.83, 1.37) C_{24} 0.94 (0.87, 1.02) ↑ Tacrolimus AUC 1.43 (1.24, 1.64) C_{max} 0.60 (0.52, 0.69) C_{12} 1.70 (1.49, 1.94) (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. Close monitoring and potential dose adjustment of tacrolimus may be required during therapy, as tacrolimus levels may decrease related to clearance of HCV.
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.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
OPIOID-SUBSTITUTION THERAPY		
Buprenorphine/naloxone		
(8 mg/2 mg single dose)/ elbasvir (50 mg single dose)	↔ Elbasvir AUC 1.22 (0.98, 1.52) C_{max} 1.13 (0.87, 1.46) C_{24} 1.22 (0.99, 1.51) ↔ Buprenorphine AUC 0.98 (0.89, 1.08) C_{max} 0.94 (0.82, 1.08) C_{24} 0.98 (0.88, 1.09) ↔ Naloxone AUC 0.88 (0.76, 1.02) C_{max} 0.85 (0.66, 1.09)	No dose adjustment is required.
(8-24 mg/2-6 mg once daily)/ grazoprevir (200 mg once daily)	↔ Grazoprevir AUC 0.80 (0.53, 1.22) C_{max} 0.76 (0.40, 1.44) C_{24} 0.69 (0.54, 0.88) ↔ Buprenorphine AUC 0.98 (0.81, 1.19) C_{max} 0.90 (0.76, 1.07)	
Methadone		
(20-120 mg once daily)/ elbasvir (50 mg once daily)	↔ R-Methadone AUC 1.03 (0.92, 1.15) C_{max} 1.07 (0.95, 1.20) C_{24} 1.10 (0.96, 1.26) ↔ S-Methadone AUC 1.09 (0.94, 1.26) C_{max} 1.09 (0.95, 1.25) C_{24} 1.20 (0.98, 1.47)	No dose adjustment is required.
(20-150 mg once daily)/ grazoprevir (200 mg once daily)	↔ R-Methadone AUC 1.09 (1.02, 1.17) C_{max} 1.03 (0.96, 1.11) ↔ S-Methadone AUC 1.23 (1.12, 1.35) C_{max} 1.15 (1.07, 1.25)	
ORAL CONTRACEPTIVES		
Ethinyl oestradiol (EE) / Levonorgestrel (LNG)		
(0.03 mg EE/ 0.15 mg LNG single-dose)/ elbasvir (50 mg once daily)	↔ EE AUC 1.01 (0.97, 1.05) C_{max} 1.10 (1.05, 1.16) ↔ LNG AUC 1.14 (1.04, 1.24) C_{max} 1.02 (0.95, 1.08)	No dose adjustment is required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90 % confidence interval) for AUC, C_{max}, C_{12} or C_{24} (likely mechanism of interaction)**	**Recommendation concerning co-administration with ZEPATIER**
(0.03 mg EE/ 0.15 mg LNG single-dose)/ grazoprevir (200 mg once daily)	↔ EE AUC 1.10 (1.05, 1.14) C_{max} 1.05 (0.98, 1.12) ↔ LNG AUC 1.23 (1.15, 1.32) C_{max} 0.93 (0.84, 1.03)	
PHOSPHATE BINDERS		
Calcium acetate (2,668 mg single dose)/ elbasvir (50 mg single dose)/ grazoprevir (100 mg single dose)	↔ Elbasvir AUC 0.92 (0.75, 1.14) C_{max} 0.86 (0.71, 1.04) C_{24} 0.87 (0.70, 1.09) ↔ Grazoprevir AUC 0.79 (0.68, 0.91) C_{max} 0.57 (0.40, 0.83) C_{24} 0.77 (0.61, 0.99)	No dose adjustment is required.
Sevelamer carbonate (2,400 mg single dose)/ elbasvir (50 mg single dose)/ grazoprevir (100 mg single dose)	↔ Elbasvir AUC 1.13 (0.94, 1.37) C_{max} 1.07 (0.88, 1.29) C_{24} 1.22 (1.02, 1.45) ↔ Grazoprevir AUC 0.82 (0.68, 0.99) C_{max} 0.53 (0.37, 0.76) C_{24} 0.84 (0.71, 0.99)	
SEDATIVES		
Midazolam (2 mg single dose)/ grazoprevir (200 mg once daily)	↔ Midazolam AUC 1.34 (1.29, 1.39) C_{max} 1.15 (1.01, 1.31)	No dose adjustment is required.
STIMULANTS		
Modafinil	Interaction not studied. *Expected:* ↓ Elbasvir ↓ Grazoprevir (CYP3A or P-gp induction)	Co-administration is contraindicated.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

If ZEPATIER is co-administered with ribavirin, the information for ribavirin with regard to contraception, pregnancy testing, pregnancy, breast-feeding, and fertility

also applies to this combination regimen (refer to the Summary of Product Characteristics for the co-administered medicinal product for additional information).

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.

Pregnancy

There are no adequate and well-controlled studies with ZEPATIER in pregnant women. Animal studies do not indicate harmful effects with respect to reproductive toxicity. Because reproduction animal studies are not always predictive of human response, ZEPATIER should be used only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

It is unknown whether elbasvir or grazoprevir and their metabolites are excreted in human milk. Available pharmacokinetic data in animals has shown excretion of elbasvir and grazoprevir in milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ZEPATIER therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of elbasvir and grazoprevir on fertility are available. Animal studies do not indicate harmful effects of elbasvir or grazoprevir on fertility at elbasvir and grazoprevir exposures higher than the exposure in humans at the recommended clinical dose (see section 5.3).

4.7 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).

4.8 Undesirable effects

Summary of the safety profile

The safety of ZEPATIER was assessed based on 3 placebo-controlled studies and 7 uncontrolled 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 3: 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 4.

Table 4: Selected treatment emergent laboratory abnormalities

Laboratory Parameters	ZEPATIER* N = 834 n (%)
ALT (IU/L)	
5.1-10.0 × ULN† (Grade 3)	6 (0.7%)
>10.0 × ULN (Grade 4)	6 (0.7%)
Total Bilirubin (mg/dL)	
2.6-5.0 × ULN (Grade 3)	3 (0.4%)
>5.0 × 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 section 4.4). The frequency of late ALT elevations was higher in subjects with higher grazoprevir plasma concentration (see sections 4.4, 4.5 and 5.2). 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

The safety assessment of Zepatier in paediatric patients aged 12 years and older is based on data from a Phase 2b, open-label clinical study that enrolled 22 patients who were treated with Zepatier for 12 weeks. The adverse reactions observed were consistent with those observed in clinical studies of Zepatier in adults.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Human experience of overdose with ZEPATIER is limited. The highest dose of elbasvir was 200 mg once daily for 10 days, and a single dose of 800 mg. The highest dose of grazoprevir was 1,000 mg once daily for 10 days, and a single dose of

1,600 mg. In these healthy volunteer studies, adverse reactions were similar in frequency and severity to those reported in the placebo groups.

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.

Haemodialysis does not remove elbasvir or grazoprevir. Elbasvir and grazoprevir are not expected to be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, Direct acting antivirals, Antivirals for treatment of HCV infections, ATC code: J05AP54.

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.

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, 3 and 4a with IC50 values ranging from 4 to 690 pM.

Antiviral activity

The EC_{50} values of elbasvir and grazoprevir against full-length or chimeric replicons encoding NS5A or NS3 sequences from reference sequences and clinical isolates are presented in Table 5.

Table 5: Activities of elbasvir and grazoprevir in GT1a, GT1b and GT4 reference sequences and clinical isolates in replicon cells

	Elbasvir	**Grazoprevir**
Reference	**EC_{50} nM**	
GT1a (H77)	0.004	0.4
GT1b (con 1)	0.003	0.5
GT4 (ED43)	0.0003	0.3
Clinical Isolates	**Median EC_{50} (range) nM**	
GT1a	0.005 (0.003 – 0.009)[a]	0.8 (0.4 – 5.1)[d]
GT1b	0.009 (0.005 – 0.01)[b]	0.3 (0.2 – 5.9)[e]
GT4	0.0007 (0.0002 – 34)[c]	0.2 (0.11 – 0.33)[a]
Number of isolates tested: a=5, b=4, c=14, d=10, e=9		

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 2,000-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 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 3- to 375-fold. In genotype 4 replicons, single NS3 substitutions D168A/V reduced grazoprevir antiviral activity by 110- to 320-fold. In general, in HCV genotype 1a, 1b or 4 replicons, combinations of grazoprevir resistance-associated substitutions further reduced grazoprevir antiviral activity.

In clinical studies
In a pooled analysis of subjects treated with regimens containing elbasvir/grazoprevir or elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical studies, resistance analyses were conducted for 50 subjects who experienced virologic failure and had sequence data available (6 with on-treatment virologic failure, 44 with post-treatment relapse).

Treatment-emergent substitutions observed in the viral populations of these subjects based on genotypes are shown in Table 6. Treatment-emergent substitutions were detected in both HCV drug targets in 23/37 (62 %) genotype 1a, 1/8 (13 %) genotype 1b and 2/5 (40 %) genotype 4 subjects.

Table 6: Treatment-emergent amino acid substitutions in the pooled analysis of ZEPATIER with and without ribavirin regimens in Phase 2 and Phase 3 clinical studies

Target	Emergent Amino Acid Substitutions	Genotype 1a N = 37 % (n)	Genotype 1b N = 8 % (n)	Genotype 4 N = 5 % (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)	100% (5)
	M/L28A/G/T/S	19% (7)	13% (1)	60% (3)
	Q30H/K/Y	14% (5)	--	--
	Q30R	46% (17)	--	--
	L/M31M/F/I/V†	11% (4)	25% (2)	40% (2)
	H/P58D‡	5% (3)	--	20% (1)
	Y93H/N/S	14% (5)	63% (5)	20% (1)
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)	40% (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)	20% (1)
	A156G/V/M	8% (3)	--	60% (3)
	V158A	5% (2)	--	--
	D168A	35% (13)	--	20% (1)
	D168C/E/G/N/V/Y	14% (5)	--	20% (1)
	V170I	--	--	20% (1)

*Reference sequences for NS5A at amino acid 28 are M (genotype 1a) and L (genotype 1b and genotype 4a and 4d).
†Reference sequences for NS5A at amino acid 31 are L (genotype 1a and genotype 1b) and M (genotype 4a and 4d).
‡Reference sequences for NS5A at amino acid 58 are H (genotype 1a) and P (genotype 1b and genotype 4a and 4d).

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.
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.

The substitutions associated with resistance to NS5B inhibitors do not affect the activity of 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 studies whose virus had treatment-emergent resistance-associated substitution in the drug target, and with available data through at least 24 weeks post-treatment using population (or Sanger) sequencing.

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

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

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

The long-term clinical impact of the emergence or persistence of virus containing ZEPATIER resistance-associated substitutions is unknown.

Effect of baseline HCV polymorphisms on treatment response

In pooled analyses of subjects who achieved SVR12 or met criteria for virologic failure, the prevalence and impact of NS5A polymorphisms (including M28T/A, Q30E/H/R/G/K/D, L31M/V/F, H58D, and Y93C/H/N) and NS3 polymorphisms (substitutions at positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175) that confer greater than 5-fold reduction of elbasvir and grazoprevir antiviral activity respectively *in vitro* were evaluated. The observed treatment response differences by treatment regimen in specific patient populations in the presence or absence of baseline NS5A or NS3 polymorphisms are summarised in Table 7.

Table 7: SVR in GT1a-, GT1b- or treatment-experienced GT4-infected subjects bearing baseline NS5A or NS3 polymorphisms

	SVR12 by Treatment Regimen			
	ZEPATIER, 12 Weeks		**ZEPATIER + RBV, 16 Weeks**	
Patient Population	**Subjects without baseline NS5A polymorphisms,* % (n/N)**	**Subjects with baseline NS5A polymorphisms,* % (n/N)**	**Subjects without baseline NS5A polymorphisms,* % (n/N)**	**Subjects with baseline NS5A polymorphisms,* % (n/N)**
GT1a†	97% (464/476)	53% (16/30)	100% (51/51)	100% (4/4)
GT1b‡	99% (259/260)	92% (36/39)		
	Subjects without baseline NS3 polymorphisms,¶ % (n/N)	**Subjects with baseline NS3 polymorphisms,¶ % (n/N)**		
GT4 (treatment-experienced)	86% (25/29)	100% (7/7)		

*NS5A polymorphisms (conferring > 5-fold potency loss to elbasvir) included M28T/A, Q30E/H/R/G/K/D, L31M/V/F, H58D, and Y93C/H/N

†Overall prevalence of GT1a-infected subjects with baseline NS5A polymorphisms in the pooled analyses was 7% (55/825)

‡Overall prevalence of GT1b-infected subjects with baseline NS5A polymorphisms in the pooled analyses was 14% (74/540)

¶NS3 polymorphisms considered were any amino acid substitution at positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175.

Overall prevalence of GT4-infected subjects with baseline NS3 polymorphisms in the pooled analyses was 19% (7/36)

Clinical efficacy and safety

The safety and efficacy of elbasvir/grazoprevir (co-administered as a fixed-dose combination; EBR/GZR) or elbasvir + grazoprevir (co-administered as single agents;

EBR + GZR) were evaluated in 8 adult clinical studies and 1 paediatric clinical study in approximately 2,000 subjects (see Table 8).

Table 8: Studies conducted with ZEPATIER

Study	Population	Study Arms and Duration (Number of Subjects Treated)	Additional Study Details
C-EDGE TN (double-blind)	GT 1, 4, 6 TN with or without cirrhosis	• EBR/GZR* for 12 weeks (N=316) • Placebo for 12 weeks (N=105)	Placebo-controlled study in which subjects were randomised in a 3:1 ratio to: EBR/GZR for 12 weeks (immediate treatment group [ITG]) or placebo for 12 weeks followed by open-label treatment with EBR/GZR for 12 weeks (deferred treatment group (DTG)).
C-EDGE COINFECTION (open-label)	GT 1, 4, 6 TN with or without cirrhosis HCV/HIV-1 co-infection	• EBR/GZR 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)	Placebo-controlled study in subjects with CKD Stage 4 (eGFR 15-29 mL/min/1.73 m2) or Stage 5 (eGFR < 15 mL/min/1.73 m2), including subjects on hemodialysis, Subjects were randomised in a 1:1 ratio to one of the following treatment groups: EBR + GZR for 12 weeks (ITG) or placebo for 12 weeks followed by open-label treatment with EBR/GZR for 12 weeks (DTG). In addition, 11 subjects received open-label EBR + GZR for 12 weeks (intensive PK arm).

Study	Population	Study Arms and Duration (Number of Subjects Treated)	Additional Study Details
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)	Multi-arm, multi-stage study. Subjects with GT 1b infection without cirrhosis were randomised in a 1:1 ratio to EBR + GZR with or without RBV for 8 weeks. TN subjects with GT 3 infection without cirrhosis were randomised to EBR + GZR with RBV for 12 or 18 weeks. TN subjects with GT 1 infection with or without cirrhosis (with or without HCV/HIV-1 co-infection) or who were peg-IFN + RBV null responders, were randomised to EBR + GZR with or without RBV for 8, 12 or 18 weeks.
C-SCAPE (open-label)	GT 4, 6 TN without cirrhosis	• EBR* + GZR* for 12 weeks (N=14) • EBR* + GZR* + RBV† for 12 weeks (N=14)	Subjects were randomised in a 1:1 ratio to the study arms.

Study	Population	Study Arms and Duration (Number of Subjects Treated)	Additional Study Details
C-EDGE TE (open-label)	GT 1, 4, 6 TE with or without cirrhosis, and with or without HCV/HIV-1 co-infection	• EBR/GZR for 12 or 16 weeks (N=105 and 105, respectively) • EBR/GZR + RBV† for 12 or 16 weeks (N=104 and 106, respectively)	Subjects were randomised in a 1:1:1:1 ratio to the study arms.
C-SALVAGE (open-label)	GT 1 TE with HCV protease inhibitor regimen‡ with or without cirrhosis	• EBR* + GZR* + RBV† for 12 weeks (N=79)	Subjects who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with peg-IFN + RBV received EBR + GZR with RBV for 12 weeks.

Study	Population	Study Arms and Duration (Number of Subjects Treated)	Additional Study Details
C-EDGE COSTAR (double-blind)	GT 1, 4, 6 TN with or without cirrhosis Opiate agonist therapy	• EBR/GZR for 12 weeks (N=201) • Placebo for 12 weeks (N=100)	Placebo-controlled study in which subjects were randomised in a 2:1 ratio to EBR/GZR for 12 weeks (ITG) or placebo for 12 weeks followed by open-label treatment with EBR/GZR for 12 weeks (DTG). Subjects were not excluded or discontinued from the trial based on a positive urine drug screen.
MK-5172A-079 (open-label)	GT 1, 4 TN or TE pediatric subjects	• EBR/GZR for 12 weeks (N=22)	Non-randomised, single-arm, open-label study in treatment-naïve or treatment-experienced pediatric subjects, including 22 subjects 12 years to less than 18 years of age, with chronic Hepatitis C (CHC) GT 1 or 4 infection without cirrhosis who received EBR/GZR for 12 weeks.

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 a fixed-dose combination; EBR + GZR = co-administered as separate single agents
[†]RBV was administered at a total daily dose of 800 mg to 1,400 mg based on weight (see section 4.2)
[‡] Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with peg-IFN + RBV

Sustained virologic response (SVR) was the primary endpoint in all studies and was defined as HCV RNA less than the lower limit of quantification (LLOQ: 15 HCV RNA IU/mL except in C-WORTHY and C-SCAPE [25 HCV RNA IU/mL]) at 12 weeks after the cessation of treatment (SVR12).

Among genotype 1b/1 other-infected subjects, the median age was 55 years (range: 22 to 82); 61% were male; 60 % were White; 20% were Black or African American; 6% were Hispanic or Latino; 82% were treatment-naïve subjects; 18% were treatment-experienced subjects; mean body mass index was 26 kg/m2; 64 % had baseline HCV RNA levels greater than 800,000 IU/mL; 22 % had cirrhosis; 71% had non-C/C IL28B alleles (CT or TT); 18 % had HCV/HIV-1 co-infection.

Treatment outcomes in genotype 1b-infected subjects treated with elbasvir/grazoprevir for 12 weeks are presented in Table 9.

Table 9: SVR in genotype 1b[†]-infected subjects[¶]

Baseline Characteristics	SVR
	EBR with GZR for 12 weeks (N = 312)
Overall SVR	96% (301/312)
Outcome for subjects without SVR	
On-treatment virologic failure[*]	0% (0/312)
Relapse	1% (4/312)
Other[‡]	2% (7/312)
SVR by cirrhosis status	
Non-cirrhotic	95% (232/243)
Cirrhotic	100% (69/69)

[†]Includes four subjects infected with genotype 1 subtypes other than 1a or 1b.
[¶]Includes subjects from C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-WORTHY and C-SURFER.
[*]Includes subjects with virologic breakthrough.
[‡]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Among genotype 1a-infected subjects, the median age was 54 years (range: 19 to 76); 71 % were male; 71 % were White; 22 % were Black or African American; 9% were Hispanic or Latino; 74% were treatment-naïve subjects; 26% were treatment-experienced subjects; mean body mass index was 27 kg/m2; 75 % had baseline HCV RNA levels greater than 800,000 IU/mL; 23 % had cirrhosis; 72% had non-C/C IL28B alleles (CT or TT); 30 % had HCV/HIV-1 co-infection.

Treatment outcomes in genotype 1a-infected subjects treated with elbasvir/grazoprevir for 12 weeks or elbasvir/grazoprevir with ribavirin for 16 weeks are presented in Table 10.

Table 10: SVR in genotype 1a-infected subjects[¶]

Baseline Characteristics	SVR	
	EBR with GZR 12 Weeks N=519	**EBR with GZR + RBV 16 Weeks N=58**
Overall SVR	93% (483/519)	95% (55/58)
Outcome for subjects without SVR		
On-treatment virologic failure[*]	1% (3/519)	0% (0/58)
Relapse	4% (23/519)	0% (0/58)
Other[‡]	2% (10/519)	5% (3/58)
SVR by cirrhosis status		
Non-cirrhotic	93% (379/408)	92% (33/36)
Cirrhotic	94% (104/111)	100% (22/22)
SVR by presence of baseline NS5A resistance-associated polymorphisms[†, §]		
Absent	97% (464/476)	100% (51/51)
Present	53% (16/30)	100% (4/4)
SVR by baseline HCV RNA		
<=800,000 IU/mL	98% (135/138)	100% (9/9)
>800,000 IU/mL	91% (348/381)	94% (46/49)

[¶]Includes subjects from C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-WORTHY and C-SURFER.
[*]Includes subjects with virologic breakthrough.
[‡]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
[†]Includes subjects with baseline sequencing data and who either achieved SVR12 or met criteria for virologic failure.
[§]GT1a NS5A polymorphisms: M28T/A, Q30E/H/R/G/K/D, L31M/V/F, H58D, and Y93C/H/N.

Among genotype 4-infected subjects, the median age was 51 years (range: 28 to 75); 66 % were male; 88 % were White; 8 % were Black or African American; 11% were Hispanic or Latino; 77% were treatment-naïve subjects; 23% were treatment-experienced subjects; mean body mass index was 25 kg/m2; 56 % had baseline HCV RNA levels greater than 800,000 IU/mL; 22 % had cirrhosis; 73% had non-C/C IL28B alleles (CT or TT); 40 % had HCV/HIV-1 co-infection.

Treatment outcomes in genotype 4-infected subjects treated with elbasvir/grazoprevir for 12 weeks or elbasvir/grazoprevir with ribavirin for 16 weeks are presented in Table 11.

Table 11: SVR in genotype 4-infected subjects[¶]

Baseline Characteristics	SVR	
	EBR with GZR 12 Weeks N=65	**EBR with GZR + RBV 16 Weeks N=8**
Overall SVR	94% (61/65)	100% (8/8)
Outcome for subjects without SVR		
On-treatment virologic failure[*]	0% (0/65)	0% (0/8)
Relapse[†]	3% (2/65)	0% (0/8)
Other[‡]	3% (2/65)	0% (0/8)
SVR by cirrhosis status		
Non-cirrhotic[§]	96% (51/53)	100% (4/4)
Cirrhotic	83% (10/12)	100% (4/4)
SVR by baseline HCV RNA		
<=800,000 IU/mL[‡]	93% (27/29)	100% (3/3)
>800,000 IU/mL[†]	94% (34/36)	100% (5/5)

[¶]Includes subjects from C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE and C-SCAPE.
[*]Includes subjects with virologic breakthrough.
[†]Both relapsers had baseline HCV RNA >800,000 IU/mL
[‡]Both subjects who failed to achieve SVR for reasons other than virologic failure had baseline HCV RNA <=800,000 IU/mL.
[§]Includes 1 subject with cirrhosis status of "unknown" in C-SCAPE.

Clinical study in subjects with advanced chronic kidney disease with genotype 1 CHC infection
In the C-SURFER study, overall SVR was achieved in 94 % (115/122) of subjects receiving EBR + GZR for 12 weeks.

Paediatric population

The efficacy of ZEPATIER was evaluated in an open-label clinical study in 22 paediatric subjects 12 years to less than 18 years of age who received ZEPATIER for 12 weeks. HCV GT1a infected subjects with one or more baseline NS5A resistance-associated substitutions were excluded from study participation.

In this study, treatment-naïve or treatment-experienced subjects 12 years to less than 18 years of age with genotype 1 or 4 CHC, without cirrhosis, were treated with ZEPATIER for 12 weeks. The median age was 13.5 years (range: 12 to 17); 50 % were female; 95 % were White; the weight range was 28.1 kg to 96.5 kg; 95.5 % had genotype 1 and 4.5 % had genotype 4; 63.6 % were treatment-naïve, 36.4 % were treatment-experienced; 45.5 % had baseline HCV RNA levels greater than 800,000 IU/mL. The overall SVR12 rate was 100 % (22/22). The safety, pharmacokinetics and efficacy observed in this study were comparable to those observed in adults.

5.2 Pharmacokinetic properties

Absorption

Following administration of elbasvir/grazoprevir 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). For elbasvir, the absolute bioavailability is estimated to be 32%. For grazoprevir, the absolute bioavailability after a 200 mg single dose ranged from 15 – 27% and after multiple 200 mg doses ranged from 20 – 40%.

Relative to fasting conditions, the administration of a single dose of elbasvir/grazoprevir with a high-fat (900 kcal, 500 kcal from fat) meal to healthy subjects resulted in decreases in elbasvir $AUC_{0\text{-}inf}$ and C_{max} of approximately 11 % and 15 %, respectively, and increases in grazoprevir $AUC_{0\text{-}inf}$ 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, elbasvir/grazoprevir may be taken without regard to food.

Elbasvir pharmacokinetics are similar in healthy subjects and HCV-infected subjects. Grazoprevir oral exposures are approximately 2-fold greater in HCV-infected subjects as compared to healthy subjects.
Based on the population pharmacokinetic modeling in non-cirrhotic, HCV-infected subjects, the geometric mean steady-state elbasvir $AUC_{0\text{-}24}$ and C_{max} at 50 mg were 2,180 nM•hr and 137 nM, respectively, and the geometric mean steady-state grazoprevir $AUC_{0\text{-}24}$ and C_{max} at 100 mg were 1,860 nM•hr and 220 nM, respectively. Following once daily administration of elbasvir/grazoprevir to HCV-infected subjects, elbasvir and grazoprevir reached steady state within approximately 6 days.

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.

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.

Metabolism

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

Excretion

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

Linearity/non-linearity

Elbasvir pharmacokinetics were approximately dose-proportional over the range of 5-100 mg once daily. Grazoprevir pharmacokinetics increased in a greater than dose-proportional manner over the range of 10-800 mg once daily in HCV-infected subjects.

Pharmacokinetics in special populations

Renal impairment
In non-HCV-infected subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m2) who were not on dialysis, elbasvir and grazoprevir AUC values were increased by 86 % and 65 %, respectively, compared to non-HCV-infected subjects with normal renal function (eGFR > 80 mL/min/1.73 m2). In non-HCV-infected subjects with dialysis-dependent, severe renal impairment, elbasvir and grazoprevir AUC values were unchanged compared to subjects with normal renal function. 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.

In population pharmacokinetic analysis in HCV-infected patients, elbasvir and grazoprevir AUCs were 25 % and 10 % higher, respectively, in dialysis-dependent patients and 46 % and 40 % higher, respectively, in non-dialysis-dependent patients with severe renal impairment compared to elbasvir and grazoprevir AUC in patients without severe renal impairment.

Hepatic impairment
In non-HCV-infected subjects with mild hepatic impairment (Child-Pugh A [CP-A], score of 5-6), elbasvir $AUC_{0\text{-}inf}$ was decreased by 40% and grazoprevir steady-state $AUC_{0\text{-}24}$ was increased 70 % compared to matched healthy subjects.

In non-HCV-infected subjects with moderate hepatic impairment (Child-Pugh B [CP-B], score of 7-9), and severe hepatic impairment (Child-Pugh C [CP-C], score of 10-15) elbasvir AUC decreased by 28 % and 12%, respectively, while the grazoprevir steady-state $AUC_{0\text{-}24}$ was increased 5-fold and 12-fold respectively, compared to matched healthy subjects (see sections 4.2 and 4.3).

Population PK analyses of HCV-infected patients in Phase 2 and 3 studies demonstrated that grazoprevir steady-state $AUC_{0\text{-}24}$ increased by approximately 65 % in HCV-infected patients with compensated cirrhosis (all with CP-A) compared to HCV-infected non-cirrhotic patients, while elbasvir steady-state AUC was similar (see section 4.2).

Paediatric population
The pharmacokinetics of elbasvir and grazoprevir have been evaluated in 22 paediatric subjects 12 years of age and older who received a daily dose of ZEPATIER (50 mg elbasvir/100 mg grazoprevir). Elbasvir and grazoprevir exposures in paediatric subjects were comparable to those observed in adults.

In paediatric subjects 12 years of age and older, the geometric mean steady-state elbasvir AUC0-24 and Cmax at 50 mg were 2,410 nM•hr and 190 nM, respectively, and the geometric mean steady-state grazoprevir AUC0-24 and Cmax at 100 mg were 1,450 nM•hr and 246 nM, respectively.

Elderly
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. These changes are not clinically relevant; therefore, no dose adjustment of elbasvir/grazoprevir is recommended based on age (see sections 4.2 and 4.4).

Gender
In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 50 % and 30 % higher, respectively, in females compared to males. These changes are not clinically relevant; therefore, no dose adjustment of elbasvir/grazoprevir is recommended based on sex (see section 4.4).

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 elbasvir/grazoprevir is recommended based on weight/BMI (see section 4.4).

Race/Ethnicity
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. These changes are not clinically relevant; therefore, no dose adjustment of elbasvir/grazoprevir is recommended based on race/ethnicity (see section 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development with grazoprevir or elbasvir. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Carcinogenicity studies for grazoprevir and elbasvir have not been conducted.

Embryo fetal and post natal development

Elbasvir

Elbasvir was given to rats and rabbits without eliciting adverse effects on embryofetal or post natal development at up to the highest doses tested (approximately 9- and 17-fold above human exposure in rats and rabbits, respectively). Elbasvir has been shown to cross the placenta in rats and rabbits. Elbasvir was excreted into the milk of lactating rats with concentrations 4-fold that of the maternal plasma concentrations.

Grazoprevir

Grazoprevir was given to rats and rabbits without eliciting adverse effects on embryofetal or post natal development at up to highest doses tested (approximately 79- and 39-fold above human exposure in rats and rabbits, respectively). Grazoprevir has been shown to cross the placenta in rats and rabbits. Grazoprevir was excreted into the milk of lactating rats with concentrations < 1-fold of the maternal plasma concentrations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Sodium laurilsulfate

Vitamin E polyethylene glycol succinate

Copovidone

Hypromellose

Microcrystalline cellulose

Mannitol (E421)

Lactose monohydrate

Croscarmellose sodium

Sodium chloride

Colloidal anhydrous silica

Magnesium stearate

Film-coating

Lactose monohydrate

Hypromellose

Titanium dioxide

Triacetin

Iron oxide yellow (E172)

Iron oxide red (E172)

Iron oxide black (E172)

Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package until use to protect from moisture.

6.5 Nature and contents of container

The tablets are packaged into a carton containing two (2) cardboard cards, each cardboard card containing (2) 7-count aluminium blisters sealed in a cardboard card for a total of 28 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (UK) Limited

120 Moorgate
London
EC2M 6UR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53095/0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

13/12/2021