ANNEX I

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 3.04 mmol (or 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 adults (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 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
The safety and efficacy of ZEPATIER in children and adolescents aged less than 18 years have not been established. No data are available.

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

The safety and efficacy of ZEPATIER have not been studied in HCV/HBV co-infected patients.

Paediatric population

ZEPATIER is not recommended for use in children and adolescents under 18 years of age because the safety and efficacy have not been established in this population.

Excipients

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

ZEPATIER contains 3.04 mmol (or 69.85 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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.

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) Cmax 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.

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**
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.
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 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)	

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**
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.
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)	
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 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)	
(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)	
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)	

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**
(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)	
(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)	
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.

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**
(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.
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.

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**
(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 (1.09, 2.00)	
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.

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**
(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)	
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.
OPIOID-SUBSTITION 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)	

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**
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.
(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.

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
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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 antiviral, ATC code: J05AX68

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 EC50 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 4replicons, 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 4subjects.

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 L/M28T/A, R/Q30E/H/R/G/K/L/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 L/M28T/A, R/Q30E/H/R/G/K/L/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 clinical studies 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).
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.
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.

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/1other-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/L/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 European Medicines Agency has deferred the obligation to submit the results of studies with ZEPATIER in one or more subsets of the paediatric populations in the treatment of chronic hepatitis C (see section 4.2 for information on paediatric use).

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).

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 Cmax at 50 mg were 2,180 nM•hr and 137 nM,

respectively, and the geometric mean steady-state grazoprevir AUC_{0-24} and Cmax 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-inf} was decreased by 40% and grazoprevir steady-state AUC_{0-24} 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_{0-24} 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_{0-24} 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/grazoprevir in paediatric patients less than 18 years of age have not been established (see section 4.2).

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
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

2 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 Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1119/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Schering-Plough Labo N.V.
Industriepark 30 - Zone A
2220 Heist-op-den-Berg
BELGIUM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

ZEPATIER 50 mg/100 mg film-coated tablets
elbasvir/grazoprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose and sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1119/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZEPATIER

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Inner wallet

1. NAME OF THE MEDICINAL PRODUCT

ZEPATIER 50 mg/100 mg film-coated tablets
elbasvir/grazoprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose and sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
MON
TUE
WED
THU
FRI
SAT
SUN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MSD + logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1119/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZEPATIER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER GLUED WITHIN THE INNER WALLET

1. NAME OF THE MEDICINAL PRODUCT

ZEPATIER
elbasvir/grazoprevir
elbasvirum/grazoprevirum

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MSD logo

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ZEPATIER 50 mg/100 mg film-coated tablets
elbasvir/grazoprevir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ZEPATIER is and what it is used for

What ZEPATIER is
ZEPATIER is an antiviral medicine that contains the active substances elbasvir and grazoprevir.

What ZEPATIER is used for
ZEPATIER is used to treat long-term hepatitis C infection in adults aged 18 years and older.

How ZEPATIER works
Hepatitis C is a virus that infects the liver. The active substances in the medicine work together by blocking two different proteins that the hepatitis C virus needs to grow and reproduce. This allows the infection to be permanently removed from the body.

ZEPATIER is sometimes taken with another medicine, ribavirin.

It is very important that you also read the leaflets for the other medicines that you will be taking with ZEPATIER. If you have any questions about your medicines, please ask your doctor or pharmacist.

2. What you need to know before you take ZEPATIER

Do not take ZEPATIER if:
- you are allergic to elbasvir, grazoprevir or any of the other ingredients of this medicine (listed in section 6)
- you have certain moderate or severe liver problems
- you are taking any of the following medicines:
  - rifampicin, usually given for tuberculosis
  - HIV protease inhibitors such as atazanavir, darunavir, lopinavir, saquinavir, or tipranavir

- efavirenz or etravirine for HIV
- elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide for HIV
- ciclosporin to stop organ transplant rejection or to treat serious inflammatory illnesses of eyes, kidney, joints or skin
- bosentan for pulmonary arterial hypertension
- carbamazepine or phenytoin, mainly used for epilepsy and seizures
- modafinil to help people who cannot stay awake
- St. John's wort (*Hypericum perforatum*, a herbal medicine) for depression or other problems.

If you are taking ZEPATIER with ribavirin, please make sure that you read the "Do not take" section of the ribavirin package leaflet. If you are unsure of any information in the package leaflet, please contact your doctor or pharmacist.

Warnings and precautions
Talk to your doctor or pharmacist before taking ZEPATIER if:
- you have ever taken any medicine for hepatitis C
- you have any liver problems other than hepatitis C
- you have had a liver transplant
- you have any other medical conditions.

Blood tests
Your doctor will test your blood before, during and after your treatment with ZEPATIER. This is so your doctor can:
- decide if you should take ZEPATIER and for how long
- decide what other medicines you should take with ZEPATIER and for how long
- check for side effects
- check if your treatment has worked and you are free of hepatitis C
- check how your liver is working - tell your doctor straight away if you have any of the following signs of liver problems: loss of appetite; feeling or being sick; feeling tired or weak; yellowing of your skin or eyes; colour changes in your stool. Your doctor may want to test your blood to check how your liver is working if you develop any of these symptoms.

Children and adolescents
ZEPATIER is not for use in children and adolescents under 18 years of age. This is because ZEPATIER has not been tested in this age group.

Other medicines and ZEPATIER
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

There are some medicines you **must not take** with ZEPATIER. See list under "Do not take ZEPATIER if you are taking any of the following medicines."

Tell your doctor or pharmacist if you take any of the following medicines:
- oral ketoconazole for fungal infections
- tacrolimus to prevent organ transplant rejection
- dabigatran to prevent blood clots
- rosuvastatin, atorvastatin, fluvastatin, simvastatin, or lovastatin, for lowering blood cholesterol.

Your doctor may have to change your medicines or change the dose of your medicines.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking ZEPATIER.

Pregnancy and contraception
The effects of ZEPATIER in pregnancy are not known. If you are pregnant, think you might be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

ZEPATIER with ribavirin
- You must not become pregnant if you are taking ZEPATIER with ribavirin. Ribavirin can be very damaging to an unborn baby. This means you and your partner must take special precautions in sexual activity if there is any chance you or your partner could become pregnant.
- You or your partner must use an effective method of contraception during treatment with ZEPATIER with ribavirin and for some time afterwards. Talk to your doctor about different contraception methods that are suitable for you.
- If you or your partner becomes pregnant while taking ZEPATIER with ribavirin or in the months that follow, tell your doctor straight away.
- It is very important that you read the information concerning pregnancy and contraception in the ribavirin package leaflet very carefully. It is important that both men and women read the information.

Breast-feeding
Talk to your doctor before taking ZEPATIER if you are breast-feeding**.** It is not known whether the two medicines in ZEPATIER pass into human breast milk.

If you are taking ZEPATIER with ribavirin, make sure that you also read the Pregnancy and Breast-feeding sections of the package leaflet for this other medicine.

Driving and using machines
Do not drive or operate machines if you feel tired after taking your medicine.

ZEPATIER contains lactose and sodium
ZEPATIER contains lactose monohydrate. If you are lactose intolerant, or if you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine. ZEPATIER contains sodium. If you are on a low sodium diet, talk to your doctor before taking this medicine.

3. How to take ZEPATIER

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Talk to your doctor or pharmacist before taking ZEPATIER if you have ever taken any medicines for hepatitis C or if you have any other medical condition.

How much to take
The recommended dose is **one tablet once a day** with or without food. Your doctor will tell you how many weeks you should take ZEPATIER for.

Swallow the tablet whole with or without food. Do not chew, crush or split the tablet. Tell your doctor or pharmacist if you have problems swallowing tablets.

If you take more ZEPATIER than you should
If you take more ZEPATIER than you should, talk to a doctor straight away. Take the medicine pack with you so that you can show the doctor what you have taken.

If you forget to take ZEPATIER
It is important not to miss a dose of this medicine. If you do miss a dose, work out how long it is since you should have taken ZEPATIER:
- If it has been less than 16 hours since you should have taken your dose, take the missed dose as soon as possible. Then take your next dose at your usual time.

- If it has been more than 16 hours since you should have taken your dose, do not take the missed dose. Wait and take your next dose at your usual time.
- Do not take a double dose (two doses together) to make up for a forgotten dose.

Do not stop taking ZEPATIER
Do not stop taking this medicine unless your doctor tells you to. It is very important that you complete the full course of treatment. This will give the medicine the best chance to treat your hepatitis C infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Tell your doctor or pharmacist if you notice any of the following side effects.

Very common: may affect more than 1 in 10 people
- feeling very tired (fatigue)
- headache

Common: may affect up to 1 in 10 people
- feeling sick (nausea)
- feeling weak or lack of energy (asthenia)
- itching
- diarrhoea
- trouble sleeping (insomnia)
- joint pain or painful, swollen joints
- constipation
- feeling dizzy
- loss of appetite
- feeling irritable
- muscle aches
- stomach pain
- unusual hair loss or thinning
- feeling nervous (anxiety)
- depression
- dry mouth
- being sick (vomiting)

Uncommon: may affect up to 1 in 100 people
- abnormalities in laboratory tests of liver function

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ZEPATIER

Keep this medicine out of the sight and reach of children.

Do not use the medicine after the expiry date which is stated on the carton and blister packaging after 'EXP'. The expiry date refers to the last day of that month.
This medicine does not require any special temperature storage conditions.
Store in the original package until use to protect from moisture.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What ZEPATIER contains

- **The active substances are:** elbasvir and grazoprevir. Each film-coated tablet contains 50 mg elbasvir and 100 mg grazoprevir.
- **The other ingredients are:**
  Tablet core:
  Sodium laurilsulfate, vitamin E polyethylene glycol succinate, copovidone, hypromellose, microcrystalline cellulose, mannitol, 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

What ZEPATIER looks like and contents of the pack
The film-coated tablets are beige, oval, debossed with "770" on one side and plain on the other. The tablet is 21 mm long and 10 mm wide.
The tablets are packaged into a carton containing two cardboard cards, each cardboard card containing two 7-count aluminium blisters. Each carton contains a total of 28 tablets.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.