Summary of risk management plan for ZEPATIER (ELBASVIR AND GRAZOPREVIR)

This is a summary of the risk management plan (RMP) for ZEPATIER. The RMP details important risks of ZEPATIER, how these risks can be minimised, and how more information will be obtained about ZEPATIER's risks and uncertainties (missing information).

ZEPATIER’s summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how ZEPATIER should be used.

This summary of the RMP for ZEPATIER should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ZEPATIER's RMP.

I. The Medicine and What It Is Used For

ZEPATIER is authorised for the treatment of chronic hepatitis C (CHC) infection in adult and paediatric patients 12 years of age and older who weigh at least 30 kg (see product labeling for the full indication). It contains elbasvir and grazoprevir as the active substance and it is given by film-coated tablet 50mg elbasvir and 100mg grazoprevir.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of ZEPATIER, together with measures to minimise such risks and the proposed studies for learning more about ZEPATIER 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of ZEPATIER is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of ZEPATIER are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ZEPATIER. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	• Drug resistance development
Important potential risks	• Emergence of Hepatocellular Carcinoma (*de novo* HCC) • Recurrence of Hepatocellular Carcinoma
Missing information	• Exposure in patients with previous hepatocellular carcinoma

II.B Summary of Important Risks

Table II.B.1: Important Identified Risk: Drug Resistance Development

Evidence for linking the risk to the medicine	Clinical studies
Risk factors and risk groups	Virologic failure after therapy with a 12 week regimen of once-daily ZEPATIER (without ribavirin) among CHC genotype 1-, genotype 4-, and genotype 6-infected subjects is rare; however, failure is often accompanied by emergence of NS3 and/or NS5A RAVs not detected prior to therapy.
Risk minimisation measures	Routine risk minimisation measures: Listed under SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical Study: Protocol 017 - A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been previously Treated with MK-5172 in a Prior Clinical Trial See section II.C of this summary for an overview of the post-authorisation development plan.

Table II.B.2: Important Potential Risk: Emergence of Hepatocellular Carcinoma (*de novo* HCC)

Evidence for linking the risk to the medicine	Literature and Clinical studies
Risk factors and risk groups	The most frequent risk factors include chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure. Cirrhosis is an important risk factor for hepatocellular carcinoma (HCC), and may be caused by chronic viral hepatitis, alcohol, inherited metabolic diseases such as hemochromatosis or alpha-1-antitrypsin deficiency, and non-alcoholic fatty liver disease. Overall, one-third of cirrhotic patients will develop HCC during their lifetime. Long-term follow-up studies have demonstrated that approximately 1–8% per year of patients with cirrhosis develop HCC (e.g. 2% in HBV-infected cirrhotic patients and 3–8% in HCV infected cirrhotic patients). In general, features of liver disease severity (low platelet count of less than 100 $X10^3$, presence of esophageal varices), in addition to older age and male gender, correlate with the risk of development of HCC among patients with cirrhosis. Other risk factors include excessive alcohol consumption, diabetes, obesity, and smoking.
Risk minimisation measures	Routine risk minimisation measures: Not applicable Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study: Protocol 149 - A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (De Novo DAA PASS) See section II.C of this summary for an overview of the post-authorisation development plan.

Table II.B.3: Important Potential Risk: Recurrence of Hepatocellular Carcinoma

Evidence for linking the risk to the medicine	Literature
Risk factors and risk groups	After resection, tumor recurrence rate exceeds 70% at 5 years including recurrence due to dissemination and *de novo* tumors. The most powerful predictors of recurrence are the presence of microvascular invasion and/or additional tumor sites besides the primary lesion. This suggests that the majority of recurrences are due to dissemination from the primary tumor and not to metachronous tumors developing in a liver with cirrhosis. Furthermore, recurrence due to dissemination is more likely to appear during the first 3 years of follow-up. In a published study, Child-Pugh Class B, more severe liver fibrosis, lower platelet count, and previous HCC were each significantly associated with HCC development, at univariate analysis. In the multivariate analysis, Child-Pugh class ($p = 0.03$, OR: 4.18, 95% CI: 1.17–14.8) and history of HCC ($p < 0.0001$, OR: 12.0, 95% CI: 4.02–35.74) were associated with HCC recurrence. Among the 59 patients with previous HCC, younger age and more severe liver fibrosis were significantly associated with HCC recurrence, both at univariate and at multivariate analysis.
Risk minimisation measures	Routine risk minimisation measures: Not applicable Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study: Protocol 135 - DAA-PASS (Category 1): A Post-Authorization Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy See section II.C of this summary for an overview of the post-authorisation development plan.

Table II.B.4: Missing Information: Exposure in Patients with Previous Hepatocellular Carcinoma

Risk minimisation measures	Routine risk minimisation measures: Not applicable Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study: Protocol 135 - DAA-PASS (Category 1): A Post-Authorization Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

Study short name

Protocol 135 - DAA-PASS (Category 1): A Post-Authorization Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy

Purpose of the study

The purpose of the DAA PASS is to estimate the risk of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name

Protocol 149 (Category 3): A study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (De Novo DAA PASS)

Purpose of the study

To evaluate the potential risk of de novo HCC after DAA treatment in HCV-infected patients with compensated cirrhosis without a history of HCC relative to patients treated with IFN-containing regimens or untreated chronic HCV patients using the US Veterans Health Administration cohort.

Study short name

Protocol 017 - A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been previously Treated with MK-5172 in a Prior Clinical Trial

Purpose of the study

The purpose of this study is to assess: 1) durability of virologic response, 2) monitor persistence of virologic resistance, and 3) long term safety.