Swiss Summary of the Risk Management Plan (RMP) of August 2021

for

Zepatier®

(Elbasvir 50mg/Grazoprevir 100mg)

Film-coated tablets

RMP Version 4.0 (September 2020)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Zepatier® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Zepatier® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

MSD Merck Sharp & Dohme AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Zepatier®.

1 Elements for Summary Tables in the EPAR

1.1 Summary Table of Safety Concerns

Table 1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Drug resistance development
Important potential risks	• Emergence of Hepatocellular Carcinoma (*de novo* HCC) • Recurrence of Hepatocellular Carcinoma
Missing information	• Exposure in pediatric patients • Exposure in patients with previous hepatocellular carcinoma

1.2 Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

Table 2 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Protocol 135 - DAA-PASS: A Post-Authorization Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy Status: Ongoing	The primary objective 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. Secondary objectives are to: 1. Compare the adjusted incidence 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; 2. 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 including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC; 3. Compare the adjusted incidence 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 including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC. The exploratory objective is to describe in a non-comparative summary the cumulative risk of HCC recurrence over time for the historical cohort alone.	Recurrence of HCC	Protocol (version 3.3) endorsed by PRAC	14-JUN-2018

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
			Amended protocol (version 4.2) endorsed by PRAC	11-JUN-2020
			Date of Final study report Submission	3Q 2021
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
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) Status: Ongoing	The primary objectives of this retrospective cohort study are as follows: 1. Estimate the risk of de novo HCC associated with DAA therapy exposure in cirrhotic HCV patients compared to no anti-HCV therapy exposure in cirrhotic HCV patients. 2. Estimate the risk of de novo HCC in cirrhotic HCV patients treated with DAA therapy compared to those treated with IFN-based therapy. The secondary objective is to compare, in a subset of patients with available data recorded in the VA CCR, tumor characteristics (i.e., tumor size, tumor number, tumor stage, tumor type) of the de novo HCC cases observed following initiation of DAA therapy to those of de novo HCC cases observed (a) following initiation of IFN-containing regimens and (b) in untreated patients.	Emergence of HCC (*de novo HCC)*	PRAC endorsed joint PASS protocol (version 3.0)	14-JUN-2019
			Date of Final Study Report Submission	14-DEC-2021
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 Status: Ongoing	Adult Population: In HCV-infected subjects who received at least 1 dose of GZR in a previous study: Objectives: To evaluate the durability of response in subjects who achieved SVR24 in the prior treatment study and at the time of entry into PN017 were HCV rRNA <lower limit of quantification (either target not detected or target detected, unquantifiable). To evaluate the presence of treatment emergent antiviral resistance to NS3/4A, NS5A and/or NS5B regions, (as applicable) and determine if there is a reversion to wild-type pattern with the 3 year time frame of this long-term follow-up study (or 5 year time frame for subjects from P052) in subjects with virologic failure in the prior treatment study and with HCV RNA ≥1000 IU/mL in P017. To evaluate the long-term safety. Pediatric Population: In HCV-infected subjects who received at least 1 dose of GZR in a previous study:	Drug resistance development	Date of initiation	April 2013
			Interim report	September 2016 (submitted September 2016)
			Date of completion	2Q 2021
			Date of Final Clinical Study Report Submission	1Q 2022

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To evaluate the persistence of treatment-emergent antiviral resistance to NS3 and NS5A regions within the 3 year time frame of this long-term follow-up study.			
Protocol 082: A Phase 1 Study to Evaluate the Bioavailability of Two MK-5172 and MK-8742 Pediatric Formulations Compared to the Adult MK-5172A Fixed-Dose Combination (FDC) Tablet in Healthy Adult Subjects Status: Ongoing	1) Primary objectives: Compare the oral bioavailability of EBR and GZR in the pediatric coated or uncoated oral granules when mixed in 1 tablespoon (15 mL) of applesauce to the oral bioavailability of EBR and GZR in the MK-5172A FDC adult tablets. 2) Secondary objective: To evaluate the safety and tolerability of single oral doses of EBR and GZR administered as the pediatric formulations in healthy participants. 3) Exploratory objective: To assess the taste of uncoated and coated EBR and GZR oral granules when mixed in 1 tablespoon (15 mL) of applesauce.	Exposure in pediatrics	Date of initiation (First patient in study)	February 2017
			Date of completion (Last Patient Last Visit)	April 2017
			Date of Final Clinical Study Report Submission	2Q 2021
Protocol 079: A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection Status: Ongoing	Primary Objective: To evaluate the steady-state EBR and GZR pharmacokinetics (PK) in children and adolescents grouped by age. Secondary Objective: To evaluate the safety and tolerability of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age. To evaluate the efficacy of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age, as assessed by the proportion of participants achieving SVR12.	Exposure in pediatrics	Date of Initiation	Jan 2018
			Date of completion (Last Patient Last Visit)	Jul 2020
			Date of Final Clinical Study Report Submission	1Q 2021

1.3 Summary of Post-authorization Efficacy Development Plan

There are no ongoing or proposed post-authorization efficacy studies (PAES) for EBR/GZR.

1.4 Summary Table of Risk Minimization Measures

Table 3 Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Drug resistance development	Routine risk communication: Listed under SmPC Section 5.1 Pharmacodynamic properties
Emergence of Hepatocellular Carcinoma (*de novo* HCC)	Routine risk communication: Not applicable.
Recurrence of Hepatocellular Carcinoma	Routine risk communication: Not applicable.
Exposure in pediatric patients	Routine risk communication: Listed under SmPC Sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties. Package leaflet – Section 2. What you need to know before you take ZEPATIER
Exposure in patients with previous hepatocellular carcinoma	Routine risk communication: Not applicable.

1.5 Additional Risk Minimization Measures

Routine risk minimisation activities as described in Part 1.4 are sufficient to manage the safety concerns of the medicinal product

2 Elements for a Public Summary

2.1 Overview of Disease Epidemiology

The Hepatitis C virus (HCV) causes liver infection that often persists for long periods of time resulting in liver inflammation (hepatitis). Over many years, continuing HCV infection may cause liver damage (cirrhosis) and/or liver cancer.

Chronic Hepatitis C (CHC) infection is a global public health challenge, affecting up to 71 million people worldwide or approximately 1% of the global population. In 2017, the WHO estimated less than 20% of persons living with CHC infection globally had been diagnosed, which corresponded to approximately 13 million people . Globally, an estimated 400,000 people die each year from CHC, mostly from liver-related complications of cirrhosis and HCC. There are 6 major CHC GTs, each with distinct sub-genotypes. GTs 1 and 3 are the most common cause of infections (44% and 25%, respectively), followed by GT 4 (15%), and GT1 and 3 infections correspond to 50-80% of

infections in North America, Latin America, and Europe.

2.2 Summary of Treatment Benefits

Grazoprevir (GZR) and elbasvir (EBR) are medicines to treat HCV infection. They are used together in a tablet that contains both medicines. A total of 4,143 individuals were given doses of GZR and/or EBR during clinical studies to demonstrate safety/efficacy of GZR and EBR. This included patients with CHC genotype 1, 4, or 6 infection, including patients who have compensated cirrhosis (scarring of the liver but with maintained liver function). In all studies, the main measure of effectiveness was the number of patients whose blood tests did not show any sign of hepatitis C virus 12 weeks after the end of treatment. In these studies, patients were given GZR/EBR, with or without ribavirin, for 8, 12 or 16 weeks, depending on the characteristics of the patients. 96% to 99% of patients given GZR/EBR tested negative for the hepatitis virus at the end of treatment. The addition of ribavirin was not needed for most patients. An additional study showed GZR/EBR to be effective in some patients with hepatitis C genotype 3 infection when given with sofosbuvir. All these studies supported the safety and efficacy of GZR/EBR for the approved use in treatment of CHC genotypes 1, 3, and 4 infections.

2.3 Unknowns Relating to Treatment Benefits

There is limited information on the use of GZR and EBR in HCV-infected patients with moderate or severe liver impairment, the use of GZR and EBR in patients less than 18 years of age, use in pregnant or breastfeeding women, use in patients who are awaiting liver transplants or recipients of liver transplantation, or use in patients who are infected with both the Hepatitis B virus and HCV at the same time.

2.4 Summary of Safety Concerns

Important Identified Risks

Table 4 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

Important Potential Risks

Table 5 Important Potential Risks: 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)

Table 6 Important Potential Risks: 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

Missing Information

Table 7 Missing Information: Exposure in Pediatric Patients

Risk minimisation measures	Routine risk minimisation measures: Listed under SmPC Sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties. Package leaflet – Section 2. What you need to know before you take ZEPATIER Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Clinical Study: Protocol 082 - A Phase 1 biocomparison and palatability study in healthy adult subjects to inform selection of age-appropriate formulations for children. Clinical Study: Protocol 079 - A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection

Table 8 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

2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine and the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The current Information for Professionals and the Patient Leaflet for Zepatier can be found on www.swissmedicinfo.ch.

This medicine has no additional risk minimization measures.

2.6 Post-Authorisation Development Plan

2.6.1 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.

2.6.2 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 Phase III Long-Term Follow-up Study

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.

Study short name
Protocol 082 - EBR and GZR Pediatric Oral Granule Formulation Bioavailability Study in Adults

Purpose of the study
The purpose of this study is to evaluate the comparative bioavailability of the EBR and GZR pediatric oral granule formulations (coated and uncoated) to that of the EBR/GZR FDC tablet in healthy adult males and females.

Study short name
Protocol 079: The Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Pediatric Patients

Purpose of the study
The purpose of this study is to assess pharmacokinetics, safety, and efficacy of ZEPATIER in a population of pediatric HCV-infected participants aged 3 years up to 18 years.

2.7 Summary of Changes to the Risk Management Plan Over Time

Table 9 Major Changes to the Risk Management Plan

RMP Version	Approval/Submission date Procedure	Change
1.3	**22-Jul-2016**	Initial RMP
2.1	**5-Jul-2017**	The following RMP safety concerns were added: Important Identified Risks • Hepatitis B Reactivation added Important Potential Risks • Emergence of Hepatocellular Carcinoma (*de novo* HCC) added • Recurrence of hepatocellular carcinoma added Missing Information • Exposure in patients with previous hepatocellular Carcinoma added • Exposure in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh B or C) removed • Exposure in patients with HBV/HCV co-infection removed The following additional pharmacovigilance was added: • A prospective safety study using data derived from a cohort of a well-defined group of patients, based on an agreed protocol will be conducted to evaluate the incidence of HCC recurrence associated with DAAs, including EBR/GZR [Important Potential Risk: Recurrence of hepatocellular carcinoma; Missing Information: Exposure in patients with previous hepatocellular carcinoma]. • An assessment will be performed to evaluate the feasibility of conducting a prospective cohort study in HCV infected patients who have compensated cirrhosis (CPT-A) and no prior history of HCC, and who are treated with DAAs, in order to estimate the impact of DAA therapies on the incidence and type (tumor characteristics) of *de novo* HCC [Important Potential Risk: Emergence of Hepatocellular Carcinoma (*de novo* HCC)]. The following additional pharmacovigilance was updated: • Milestones/due dates were updated for Protocol 079
3.1	**12-Oct-2020**	Descriptions and/or milestones of Category 1 (Protocol 135) and Category 3 Protocols 149, 017, 082 and 079) studies in the Pharmacovigilance (PV) Plan have been updated. The risk profile of elbasvir and grazoprevir was reevaluated based upon EMA GVP Module V – Risk Management Plan (revision 2) guidance. The MAH removed the following Important Identified Risks and Missing Information: Important Identified Risks • Hepatitis B Virus Reactivation • Late ALT Elevation • Hyperbilirubinemia • Drug interactions with CYP3A inducers; OATP1B inhibitors; strong CYP3A inhibitors; fixed dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate or alafenamide; atorvastatin, rosuvastatin, lovastatin, simvastatin, fluvastatin; and tacrolimus Missing Information • Exposure in pregnant or lactating women • Exposure in liver transplant patients

RMP Version	Approval/Submission date Procedure	Change
4.0	**xx-xxx-xxxx**	In Part III, Sections III.2 and III.3, the objectives of Protocol 135-DAA PASS (Category 1), were updated to include the exploratory objective ("The exploratory objective is to describe in a noncomparative summary the cumulative risk of HCC recurrence over time for the historical cohort alone.") In Part III, Section III.2 the milestones for Protocol 082 were updated to include the planned date for the Final Clinical Study Report Submission (2Q 2021) to be consistent with the information provided for Protocol 082 in Section III.3.