Swiss Summary of the Risk Management Plan (RMP)

for

Harvoni®

(Ledipasvir / Sofosbuvir)
(LDV / SOF)

Version 5.0 (December 2020)

Based on EU RMP v8.0

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1. SUMMARY OF RISK MANAGEMENT PLAN FOR HARVONI (LEDIPASVIR/SOFOSBUVIR)

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 minimize them.

The RMP summary of Harvoni 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 Harvoni in Switzerland is the „Arzneimittelinformation / Information sur le médicament“ (see www.swissmedic.ch) approved and authorized by Swissmedic.

Gilead Sciences Switzerland Sàrl is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Harvoni.

1.1. The Medicine and What is it Used for

Harvoni is authorized for the treatment of chronic hepatitis C (CHC) in adults and in pediatric patients aged 3 years and above (see SmPC for the full indication). It contains sofosbuvir (SOF) and ledipasvir (LDV) as active substances and it is given orally.

Further information about the evaluation of Harvoni’s benefits can be found in Harvoni’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/harvoni.

1.2. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Harvoni, together with measures to minimize such risks and the proposed studies for learning more about Harvoni’s risks, are outlined below.

Measures to minimize 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 authorized 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 public (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Harvoni, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (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 Harvoni is not yet available, it is listed under 'missing information' below.

1.2.1. List of important risks and missing information

Important risks of Harvoni are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. 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 Harvoni. 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 0-1. List of Important Risks and Missing Information

Important Identified Risks	Severe bradycardia and heart block when used with concomitant amiodarone
	HBV reactivation in HBV/HCV coinfected patients
Important Potential Risks	Recurrence of HCC
	Emergence of HCC
Missing Information	Safety in patients with previous HCC

1.2.2. Summary of Important Risks

Table 0-1. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**Severe bradycardia and heart block when used with concomitant amiodarone**
Evidence for linking the risk to the medicine	Cases of severe bradycardia and heart block have been observed when Harvoni is used in combination with amiodarone with or without other drugs that lower heart rate. Cases are potentially life threatening.
Risk factors and risk groups	Patients also taking beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone.
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC Sections 4.4, 4.5, and 4.8 PL Section 2 Additional risk minimization measures: None

Important Identified Risk	**HBV reactivation in HBV/HCV coinfected patients**
Evidence for linking the risk to the medicine	Cases of HBV reactivation have been reported in patients coinfected with HBV/HCV during or after treatment with DAAs. HBV reactivation can potentially be life-threatening, as it could result in hepatitis, an increase in transaminase levels, an increase in bilirubin levels, hepatic failure and death.
Risk factors and risk groups	Due to the small number of cases of HBV reactivation with DAAs, risk factors have not been definitively established. However, some of the cases involving HBV reactivation with SOF-containing regimens involved patients who were immunocompromised (patients coinfected with HIV or patients receiving immunosuppressants due to prior transplant). In addition, a case involving severe HBV reactivation had risk factors of NASH and Burkitt's lymphoma.
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC Section 4.4 PL Section 2 Additional risk minimization measures: None
Important Potential Risk	**Recurrence of HCC**
Evidence for linking the risk to the medicine	HCC has been reported in some patients who have previously had HCC while taking drugs used to treat hepatitis C virus (direct acting antivirals). It is unclear whether hepatitis C direct acting antivirals increase the risk of HCC returning in patients who previously had HCC and a study is being conducted to investigate this. The risk has not yet been confirmed.
Risk factors and risk groups	Risk factors associated with HCC recurrence include high alpha-fetoprotein (AFP) levels prior to HCC treatment, the size of the primary tumor, and the number of primary tumors. The risk of recurrence will also depend on the method used to treat the primary tumor.
Risk Minimization Measure(s)	No risk minimization measures
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: A study to assess the impact of DAA treatment on the incidence of HCC recurrence, relative to no DAA therapy. See Section 1.2.3 of this summary for an overview of the post-authorization development plan.
Important Potential Risk	**Emergence of HCC**
Evidence for linking the risk to the medicine	Some patients have developed HCC while taking drugs used to treat hepatitis C virus (direct acting antivirals). HCC is a known complication of hepatitis C virus especially in the presence of advanced liver disease. It is unclear whether hepatitis C direct acting antivirals increase the risk of developing HCC or not. The risk has not yet been confirmed.
Risk factors and risk groups	The presence of cirrhosis is a primary major risk factor for the development of HCC in CHC patients {Lok et al 2009}. Additional risk factors for the development of HCC in CHC patients includes older age, male sex, heavy alcohol use, diabetes, obesity, smoking, and HBV-coinfection {El-Serag et al 2007, Hiramatsu et al 2015, Shariff et al 2009, Yang et al 2010}. Clinical factors shown to influence the risk of HCC include advanced liver fibrosis, lower platelet count and albumin level; higher levels of alkaline phosphatase and α-fetoprotein; and the presence of esophageal varices {Hiramatsu et al 2015, Lok et al 2009}. In CHC patients treated with DAAs, the presence of cirrhosis and treatment failure were associated with an increased risk of de

	novo HCC; treatment with DAAs with or without IFN was not a risk factor for de novo HCC.
Risk Minimization Measure(s)	No risk minimization measures The need for risk minimization measures will be reassessed following the availability of results from an investigation of the impact of DAA therapies on the incidence and type of de novo HCC.
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Study to evaluate the risk of de novo HCC in patients with compensated cirrhosis treated with DAAs for chronic hepatitis C. See Section 1.2.3 of this summary for an overview of the post-authorization development plan.
Missing information	**Safety in patients with previous HCC**
Risk Minimization Measure(s)	No risk minimization measures The need for risk minimization measures will be reassessed following the availability of the results from a study for HCC recurrence.
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Study to assess the impact of DAA treatment on the incidence of HCC recurrence, relative to no DAA therapy See Section 1.2.3 of this summary for an overview of the post-authorization development plan.

1.2.3. Post-authorization Development Plan

1.2.3.1. Studies which are Conditions of the Marketing Authorization

Table 0-1. Studies as Condition of the Marketing Authorization

Short Study Name	Purpose of the Study
DAA-PASS: A post-authorisation safety study of early recurrence of hepatocellular carcinoma in HCV-infected patients after direct-acting antiviral therapy	To evaluate the impact of DAA treatment on the incidence of HCC recurrence, relative to no DAA therapy

1.2.3.2. Other Studies in Post-Authorization Development Plan

Table 0-1. Other Studies in Post-Authorization Development Plan

Short Study Name	Purpose of the Study
De Novo DAA PASS: 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	To evaluate among compensated cirrhotic patients, whether DAA therapy for chronic HCV infection increases the risk of incident HCC compared to no treatment or treatment with IFN-based regimens

This summary was last updated in December 2020.