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

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

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

This summary of the RMP for Harvoni 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 Harvoni's RMP.

I. 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 SmPCs 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.

II. 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.

II.A. 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 Part VI.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	None
Missing Information	None

II.B. Summary of Important Risks

Table Part VI.2. 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	**None**
Missing information	**None**

II.C. Post-authorization Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or a specific obligation of Harvoni.

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

There are no studies required for Harvoni.