PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR EPCLUSA (SOFOSBUVIR/VELPATASVIR)

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

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

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

1.1. The Medicine and What is it Used for

Epclusa is authorized for treatment of chronic hepatitis C (CHC) in adults (see SmPC for the full indication). It contains sofosbuvir (SOF) and velpatasvir (VEL) as active substances and it is given orally.

Further information about the evaluation of Epclusa's benefits can be found in Epclusa's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage.

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

Important risks of Epclusa, together with measures to minimize such risks and the proposed studies for learning more about Epclusa'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 minimizes its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed 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 Epclusa is not yet available, it is listed under 'missing information' below.

1.2.1. List of important risks and missing information

Important risks of Epclusa 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 Epclusa. 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 1-1. 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 pregnant women
	Safety in HCV patients with severe renal impairment or ESRD
	Development of resistance
	Safety in patients with previous HCC

1.2.2. Summary of Important Risks

Table 1-2. 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 have been observed when SOF-containing regimens are used in combination with amiodarone.
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 section 4.4, 4.5,and 4.8 PL section 2. Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: 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
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: 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. 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.
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. 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. 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. 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: Investigation of the impact of DAA therapies on the incidence and type of de novo HCC. See Section 1.2.3 of this summary for an overview of the post-authorization development plan.
Missing information	**Safety in pregnant women**
Risk Minimization Measure(s)	Routine risk minimization measures SmPC section 4.6 PL section 2. Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: None
Missing information	**Safety in HCV patients with severe renal impairment or ESRD**
Risk Minimization Measure(s)	Routine risk minimization measures SmPC Sections 4.2, 4.4, and 5.2 PL Section 2 Additional risk minimization measures: None

Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Studies in HCV-infected subjects with severe renal insufficiency (GS-US-342-4062 and GS-US-337-4063). See Section 1.2.3 of this summary for an overview of the post-authorization development plan.
Missing information	**Development of resistance**
Risk Minimization Measure(s)	Routine risk minimization measures: None Additional risk minimization measures: None No risk minimization measures are considered necessary for the development of resistance at this time. Clinical data suggest that the presence of an NS5A RAV does not preclude successful retreatment.
Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Long term follow-up registry study of subjects who did not achieve sustained virologic response in Gilead-sponsored trials in subjects with chronic hepatitis C infection (GS-US-248-0123) 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 planned 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 1-3. 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 1-4. Other Studies in Post-Authorization Development Plan

Short Study Name	Purpose of the Study
GS-US-342-4062 A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir for 12 Weeks in Subjects with Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease	To evaluate the safety, efficacy and PK of SOF/VEL in subjects who are on dialysis for end stage renal disease (ESRD)
GS-US-337-4063 A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Ledipasvir/Sofosbuvir in Subjects with Genotype 1, 4, 5 and 6 Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease	To evaluate the safety, efficacy and PK of LDV/SOF for 8, 12 or 24 weeks in subjects who are on dialysis for end stage renal disease (ESRD)
GS-US-248-0123 A Long Term Follow-up Registry Study of Subjects Who Did Not Achieve Sustained Virologic Response in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection	To evaluate HCV viral sequences and the persistence or evolution of treatment-emergent viral mutations in subjects who fail to achieve an SVR after treatment with a Gilead oral antiviral containing regimen in a previous Gilead-sponsored hepatitis C study
Investigation of the impact of DAA therapies on the incidence and type of de novo HCC	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