SUMMARY OF RISK MANAGEMENT PLAN FOR MYHEP ALL (SOFOSBUVIR/ VELPATASVIR) - VERSION 2.0

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

MyHep ALL Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how MyHep ALL should be used.

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

I. The medicine and what it is used for

MyHep ALL is authorised for the treatment of chronic hepatitis C (HCV) infection in adults. It contains sofosbuvir/velpatasvir as the active substance and it is given by oral route of administration.

II. Risks associated with the medicine and activities to minimize or further characterize the risks.

Important risks of MyHep ALL, together with measures to minimize such risks and the proposed studies for learning more about MyHep ALL'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 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 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 events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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II.A List of important risks and missing information

Important risks of MyHep ALL are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered by patients. 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 MyHep ALL. 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/use in special patient populations etc.);

List of important risks and missing Information	
Important identified risks	• Severe bradycardia and heart block when used with concomitant amiodarone • Hepatitis B reactivation in HBV/HCV co-infected patients
Important potential risks	• Recurrence of HCC • Emergence of HCC
Missing information	• Safety in pregnant women • Development of resistance • Safety in patients with previous HCC

II.B Summary of important risks

Important identified risk: Severe bradycardia and heart block when used with concomitant amiodarone	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
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 measures	Routine risk communication: • SmPC Sections 4.4, 4.5, and 4.8 Additional risk minimization measures: • None

Important identified risk: HBV reactivation in HBV/HCV coinfected patients	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.

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 measures	Routine risk minimization measures: • SmPC Sections 4.4 Additional risk minimization measures: • None

Important potential risks-Recurrence of HCC	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important potential risk
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 measures	None

Important potential risks-Recurrence of HCC	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important potential risk
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 measures	None

Missing information- Safety in pregnant women	
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.6 Additional risk minimization measures: • None

Missing Information -Development of resistance	
Risk minimization measures	None

Missing Information -Safety in patients with previous HCC	
Risk minimization measures	None

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization.

No studies are conditions of the marketing authorization or specific obligations of MyHep ALL.

II.C.2 Other studies in post-authorization development plan

Not applicable.