SUMMARY OF RISK MANAGEMENT PLAN FOR HEPCLUDEX (BULEVIRTIDE)

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

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

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

I. The Medicine and What is it Used for

Hepcludex is authorised for chronic hepatitis delta (CHD) – (see SmPC for the full indication). It contains bulevirtide as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Hepcludex's benefits can be found in Hepcludex's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage*:*

https://www.ema.europa.eu/en/medicines/human/EPAR/Hepcludex

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of Hepcludex, together with measures to minimise such risks and the proposed studies for learning more about Hepcludex's risks, are outlined below.

Measures to minimise 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 minimises its risks.

Together, these measures constitute routine risk minimisation measures.

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

II.A. List of Important Risks and Missing Information

Important risks of Hepcludex are risks that need special risk management activities to further investigate or minimise 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 Hepcludex. 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	Hepatitis exacerbation after drug discontinuation
Important Potential Risks	None
Missing Information	Use in patients with moderate or severe renal impairment
	Use in patients with decompensated liver disease
	Long term safety of bile acid elevation

II.B. Summary of Important Risks

Hepcludex has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should be initiated by a doctor experienced in the management of hepatitis D virus infection (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**Hepatitis exacerbation after drug discontinuation**
Evidence for linking the risk to the medicine	Pronounced reactions were reported only in a few participants who had been exposed to bulevirtide for 12-24 weeks. The events were observed at the follow-up visits after the end of trial treatment and most had no major clinical symptoms or decompensation. The reactions to antiviral drug discontinuation are anticipated and are routinely noted in other chronic viral diseases, like hepatitis B virus (HBV) monoinfection and human immunodeficiency virus (HIV) infection.
Risk factors and risk groups	The exacerbation occurs after cessation of bulevirtide and leads to a slow increase of HBV DNA, hepatitis D virus (HDV) RNA, and alanine aminotransferase (ALT) levels to baseline. So far, no dose relatedness or additive factors have been detected.
Risk Minimization Measure(s)	Routine risk minimization measures SmPC section 4.4. where advice is given on monitoring of HBV DNA, HDV RNA, and transaminase levels after the cessation of bulevirtide. SmPC section 4.8 PL sections 2 and 3 Additional risk minimization measures None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: MYR204 - A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta See Section II.C of this summary for an overview of the postauthorization development plan.
Missing information	**Use in patients with moderate or severe renal impairment**
Risk Minimization Measure(s)	Routine risk minimization measures SmPC sections 4.8 and 5.2 SmPC section 4.2 and PL section 2, where advice is given on the monitoring of renal function Additional risk minimization measures: None
Missing information	**Use in patients with decompensated liver disease**
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

Missing information	Long term safety of bile acid elevation
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC section 4.8 PL section 4 Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: MYR204 - A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta: additional monitoring for vitamin D levels and blood lipids MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta: additional monitoring for vitamin D levels and blood lipids GS-US-589-6206 - A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization 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 specific obligation of Hepcludex.

II.C.2. Other Studies in Postauthorization Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
GS-US-589-6206 – A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection	This current Registry study aims to collect postmarketing data from patients with chronic HDV infection who are treated with bulevirtide in countries where it is approved to create a unique clinical database to evaluate the safety and long-term effects of bulevirtide treatment on clinical progression of liver disease through the incidence of liver-related events. Primary objective: • To evaluate the long-term effects of bulevirtide treatment on clinical progression of liver disease through the incidence of liver-related events in participants treated with bulevirtide Secondary objectives: • To evaluate the development of cirrhosis in participants treated with bulevirtide who were previously noncirrhotic • To evaluate the safety of participants treated with bulevirtide

Short Study Name	Purpose of the Study
MYR204 - A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta	Pegylated interferon alfa -2a (PEG-IFN alfa) is approved for treatment of chronic HBV infection, which is required for the propagation of HDV, and used to treat patients with HDV infection with evidence of some virologic efficacy. A combination of bulevirtide with PEG-IFN alfa demonstrated significant synergistic effects in previous clinical trials (e.g., MYR203). It is therefore warranted to further investigate the combination therapy with the aim of improvement of sustained virologic response rates. Primary objectives: • The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously at a dose of 2 mg or 10 mg in combination with pegylated interferon alfa-2a once weekly relative to 10 mg bulevirtide monotherapy in subjects with chronic hepatitis delta (CHD). Secondary objectives: • To assess the safety of bulevirtide Exploratory objectives: • To investigate the immunogenicity of bulevirtide • To investigate the influence of bulevirtide on quality of life • HBV/HDV genotyping • Resistance testing
MYR301 – A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta	This study is designed to assess the long-term efficacy and safety of bulevirtide in patients with CHD. Primary efficacy and safety data will be assessed at Week 48, when bulevirtide at 2 and 10 mg daily doses will be compared with delayed treatment. After Week 48, patients of the delayed treatment arm in this study will be switched to bulevirtide at 10 mg daily dose for additional 96 weeks. The total duration of treatment period in this Phase 3 study will be 144 weeks. Primary objectives: • The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta in comparison to delayed treatment. Secondary objectives: • To evaluate optimal treatment duration • To assess the safety of bulevirtide Exploratory objectives: • To investigate the immunogenicity of bulevirtide • To investigate the influence of bulevirtide on quality of life • HBV/HDV genotyping • Resistance testing