Summary of risk management plan for BARACLUDE (entecavir)

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

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

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

I. The medicine and what it is used for

BARACLUDE is authorised for CHB infection (see SmPC for the full indication). It contains entecavir as the active substance and it is given orally.

Further information about the evaluation of entecavir's benefits can be found in BARACLUDE'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/baraclude.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of BARACLUDE, together with measures to minimise such risks and the proposed studies for learning more about BARACLUDE'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 health care 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 patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk-minimisation* measures.

If important information that may affect the safe use of BARACLUDE is not yet available, it is listed under 'Missing information' below.

II.A List of important risks and missing information

Important risks of BARACLUDE are risks that need special risk-management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 BARACLUDE. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	ETV resistance
	Exacerbation of hepatitis (ALT increase/hepatic flare)
	Emergence of resistant HIV in HIV/HBV coinfected patients
Important potential risks	Mitochondrial toxicity (including lactic acidosis)
Missing information	Use in pregnancy
	Use in patients with severe acute exacerbation of CHB

II.B Summary of important risks

Important identified risk

ETV Resistance	
Evidence for linking the risk to the medicine	Scientific literature, CCDS
Risk factors and risk groups	*LVD-refractory patients:* Mutations in the HBV polymerase that encode LVDr substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with ETVr. Patients with LVDr HBV are at higher risk of developing subsequent ETVr HBV than patients not previously treated with LVD. Virologic response should be closely monitored in the LVD-refractory population, and appropriate resistance testing should be performed. In patients with decompensated liver disease, virologic breakthrough may be associated with serious clinical complications of the underlying liver disease. Therefore, in patients with both decompensated liver disease and LVDr HBV, combination use of ETV plus a second antiviral agent (that does not share cross-resistance with either LVD or ETV) should be considered in preference to ETV monotherapy.

Important identified risk

	Reduction of HBV DNA to < 300 copies/mL correlated strongly with maintenance of the HBV DNA response during continued treatment and with an absence of resistance.
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Section 4.4 and recommended dosing in Section 4.2.
Exacerbation of Hepatitis (ALT Increase/Hepatic Flare)	
Evidence for linking the risk to the medicine	Scientific literature.
Risk factors and risk groups	Underlying cirrhosis (hepatic decompensation); HBV pre-S deletion precore mutations before treatment (with LVD); higher pretreatment ALT (HBeAg-positive); LVD-resistant virus with rebound viraemia; HCV/HDV coinfection during treatment with interferon and ribavirin; expansion of HBV-specific memory cells (CD8 T-cells); robust immune response; decreased CD4 T-cell count in HIV coinfected patients; concurrent chemotherapy; and emergence of precore mutants in late HBV infection.
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Sections 4.4 and 4.8.
Emergence of Resistant HIV in HIV/HBV Coinfected Patients	
Evidence for linking the risk to the medicine	In vitro assessment of ETV against HIV, Clinical Overview, scientific literature
Risk factors and risk groups	HIV/HBV coinfected patients not receiving effective concomitant HAART.
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Section 4.4.

Important potential risk

Mitochondrial Toxicity (Including Lactic Acidosis)	
Evidence for linking the risk to the medicine	Scientific literature
Risk factors and risk groups	Adult “mitochondrial disease” syndromes occur most likely in genetically susceptible individuals, brought out by the stress of NRTI therapy; such patients may also have a positive family history for similar events. Neither the prevalence of relevant genetic changes nor their potential impact is completely understood. In patients with chronic liver disease, LA may result from both increased lactate production and decreased hepatic lactate clearance in patients with cirrhosis; increased lactate production may result from tissue hypoperfusion or compromised cellular oxygen metabolism, while decreased lactate clearance may result from a lack of functioning hepatocytes. Individuals with advanced hepatic cirrhosis are expected to maintain a fragile acid-base balance and to experience impaired ability for lactate disposal because of a relative lack of functioning hepatocytes. In addition, most of the identified patients also had significant relevant comorbidities. It is therefore considered likely that the severity of the

	underlying hepatic disease, as well as the relevant comorbidities, may have had a causal role and/or could provide an alternative explanation for the development of LA in the majority of cases. The relatively high frequency of underlying cirrhosis, hepatic decompensation, or acute liver failure observed in the patients described in the postmarketing case reports of LA or increased lactic acid received to date suggests that patients with these conditions may be at specific increased risk for lactate-associated AEs. Many cases were also noted to be confounded by relevant comorbidities (eg, diabetes) and/or concomitant medications (eg, metformin).
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Section 4.4

Missing information

Use in Pregnancy	
Evidence for linking the risk to the medicine	There are no adequate and well-controlled studies in pregnant women. ETV should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Risk-minimisation measures	Routine risk-minimisation measures: SmPC description in Section 4.6.

Use in Patients with Severe Acute Exacerbation of CHB	
Evidence for linking the risk to the medicine	In a retrospective analysis, a higher 1-year mortality rate with ETV was identified when compared with LVD in a specific subset of patients in whom therapy was initiated during a spontaneous severe acute exacerbation of CHB infection. Although this analysis suggested that ETV was associated with an increased mortality at 1 year, the excess mortality was accounted for by deaths in the first 30 days of treatment. In contrast, 3 other retrospective analyses of ETV- versus LVD-treated patients with an acute spontaneous exacerbation of CHB revealed a similar response with both treatments and no increases in mortality during treatment at specific time points of 4 weeks and 6 months.
Risk-minimisation measures	Routine risk-minimisation measures: SmPC warnings in Section 4.4.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of BARACLUDE.

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

There are no studies required for BARACLUDE.