	minimisation measures: Prescription only medicine	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. The virus is transmitted through contact with the blood or other body fluids of an infected person.
Hepatitis B infection may be either short-lived (acute) lasting less than six months or long lasting (chronic) that lasts six months or longer and may lead to serious illnesses such as cirrhosis and liver cancer
An estimated 240 million people are chronically infected with hepatitis B (defined as hepatitis B surface antigen positive for at least 6 months).
The overall prevalence of HBsAg is reported to be 3.6 percent; however, it varies depending upon the geographic area. The prevalence of chronic HBV ranges from <2 percent in low prevalence areas (eg, United States, Canada, Western Europe) to 2 to 7 percent in intermediate prevalence areas (eg, Mediterranean countries, Japan, Central Asia, Middle East, and parts of South America) to ≥8 percent in high prevalence areas (eg, Western Africa, South Sudan).

VI.2.2 Summary of treatment benefits

Entecavir is a guanosine nucleoside analogue with activity against HBV polymerase. It is used in adults with signs of ongoing liver injury (such as inflammation and fibrosis) when the liver is still working properly (compensated liver disease) and also when the liver is no longer working properly (decompensated liver disease). It can also be considered for children aged from 2 to 18 years but only in those with compensated liver disease
Three main studies in adults with chronic hepatitis B who had compensated liver disease have been performed. Two of the studies were carried out in 1,363 patients who had not been treated with nucleoside analogues before. The third study was carried out in 293 patients whose infection was no longer responding to lamivudine treatment. The scope of the studies was to determine how the liver damage had evolved after 48 weeks treatment by examining samples of liver tissue and measuring signs of the disease such as the levels of a liver enzyme (ALT) or viral DNA in the blood.

In another study, entecavir was compared with another medicine, adefovir dipivoxil, in 195 patients with chronic hepatitis B with decompensated liver disease. The scope of this study was to determine the reduction in viral DNA in the blood after 24 weeks.

Finally, a study in paediatric population has also performed. 180 children aged 2 to 18 years who had chronic hepatitis B were randomly selected to be given either Entecavir or placebo (a dummy treatment). The scope of this study was to determine the reductions in levels of the virus in the blood and the number of patients who developed antibody to a viral protein (known as e-antigen) and no longer had e-antigen in their blood after 48 weeks of treatment.

VI.2.3 Unknowns relating to treatment benefits

There is not much information about entecavir safety on long term use. However, Bristol-Myers Squibb Pharma EEI, the MAH of the originator product Baraclude has completed 2 entecavir (ETV) studies (AI463049, and AI463901) to allow for long term follow up of ETV treated patients, to assess for potential risk of malignant neoplasms and other long term complications. A third study AI463080 is ongoing.

A publication by Wong et al. identified a higher 1 year mortality rate with entecavir compared to lamivudine in a specific subset of patients with spontaneous severe acute exacerbation of chronic hepatitis B. Bristol-Myers Squibb Pharma EEI, the MAH of the originator product Baraclude, has continued to review the literature during its routine PhV activities in order to identify other relevant publications No further publications have been identified that indicate a potential for increase in liver specific mortality with entecavir treatment.

There are no adequate and well controlled studies in pregnant woman. Therefore, entecavir should not be used during pregnancy unless clearly necessary. Furthermore, women of child-bearing potential should use effective contraception,

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Aggravation of hepatitis *(Exacerbation of hepatitis)*	Aggravation of hepatitis B occurs commonly (affects at least 1 in 100 patients who take entecavir) and is characterised by increased blood levels of liver enzymes.	In patients with hepatitis B treated with entecavir, blood levels of liver enzymes should be monitored closely during therapy but also at least 6 months after discontinuation of hepatitis B therapy.
Development of resistance to entecavir treatment *(Entecavir resistance)*	Entecavir is an antiviral belonging to the class of the nucleoside analogues. Entecavir interferes with the action of a viral enzyme, DNA polymerase, which is involved in the formation of viral DNA. Entecavir stops the virus making DNA, and prevents it from	Patients treated with entecavir should be closely monitored

	multiplying and spreading. However, in cell culture as well as in clinical studies mutations have been reported making subject resistant to entecavir therapy. This may lead to serious clinical complications on the underlying liver disease	
Development of resistant on Human Immunodeficiency Virus in Human Immunodeficiency Virus / Chronic Hepatitis B virus (HIV/HBV) co-infected patients not concurrently receiving effective HIV treatment *(Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment)*	Entecavir has not been evaluated in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment. Development of HIV resistance has been observed when entecavir was used to treat chronic hepatitis B infection in patients with HIV infection not receiving highly active antiretroviral therapy.	Therefore, therapy with entecavir should not be used for HIV/HBV co-infected patients who are not receiving highly active antiretroviral therapy. Entecavir has not been studied as a treatment for HIV infection and is not recommended for this use

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Carcinogenicity	Two-year carcinogenicity studies in male mice, revealed increases in the frequencies of lung tumours at exposures ≥ 4 and ≥ 2 times that in humans at 0.5 mg and 1 mg respectively. Tumour development was preceded by pneumocyte proliferation in the lung which was not observed in rats, dogs, or monkeys, indicating that a key event in lung tumour development observed in mice likely was species-specific. Increased incidences of other tumours including brain gliomas in male and female rats, liver carcinomas in male mice, benign vascular tumours in female mice, and liver adenomas and carcinomas in female rats were seen only at high lifetime exposures. However, the no effect levels could not be precisely established. The predictivity of the findings for humans is not known.
Development of toxicity to mitochondria *(Mitochondrial toxicity)*	Mitochondria are specialized compartments present in every cell of the body except red blood cells. Mitochondria are responsible for creating more than 90% of the energy needed by the body to sustain life and support growth. When they fail, less and less energy is generated within the cell. Cell injury and even cell death follow.

	Diseases of the mitochondria appear to cause the most damage to cells of the brain, heart, liver, skeletal muscles, kidney and the endocrine and respiratory systems. Depending on which cells are affected, symptoms may include loss of motor control, muscle weakness and pain, gastro-intestinal disorders and swallowing difficulties, poor growth, cardiac disease, liver disease, diabetes, respiratory complications, seizures, visual/hearing problems, lactic acidosis, developmental delays and susceptibility to infection

Missing information

Risk	**What is known**
Long term safety and clinical outcomes data	Data on long term safety is not available. However, Bristol-Myers Squibb Pharma EEI, the MAH of the originator product Baraclude has completed 2 entecavir (ETV) studies (AI463049, and AI463901) to allow for long term follow up of ETV treated patients, to assess for potential risk of malignant neoplasms and other long term complications. A third study AI463080 is ongoing.
Use in the paediatric population	There is no adequate data on safety and efficacy of long-term use of entecavir to paediatric population
Use in pregnancy	*Pregnancy:* there are no adequate data from the use of entecavir in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Entecavir should not be used during pregnancy unless clearly necessary. There are no data on the effect of entecavir on transmission of HBV from mother to newborn infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV. *Women of childbearing potential:* given that the potential risks to the developing foetus are unknown, women of childbearing potential should use effective contraception.
Use in elderly patients (≥ 65 years old)	The pharmacokinetic profile of entecavir does not differ by age. No dosage adjustment based on age is required. The dose should be adjusted according to the patient's renal function. However, the risk of toxic reactions to entacavir may be greater in elderly patients, because entecavir is substantially excreted by the kidney and elderly are more likely to have decreased renal function
Use in severe acute exacerbation of chronic hepatitis B	A publication by Wong et al. identified a higher 1 year mortality rate with entecavir compared to lamivudine in a specific subset of patients with spontaneous severe acute exacerbation of chronic hepatitis B. Bristol-Myers Squibb Pharma EEI, the MAH of the originator product Baraclude, has continued to review the literature during its routine

	PhV activities in order to identify other relevant publications No further publications have been identified that indicate a potential for increase in liver specific mortality with entecavir treatment.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change
1.0	28.06.2016	**Important identified risks** • Exacerbation of hepatitis • Entecavir resistance • Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment **Important potential risks** • Carcinogenicity • Mitochondrial toxicity **Missing information** • Long term safety and clinical outcomes data • Use in the paediatric population • Use in pregnancy • Use in elderly patients (≥ 65 years old) • Use in severe acute exacerbation of chronic hepatitis B (CHB)	Initial version

1.0	20.02.2017		Responses to Day 70 RMS Preliminary As-sessment Report
1.0	16.05.2017		Responses to Day 120 RMS Preliminary Assessment Report. SmPC and PIL update
1.0	07.06.2017		Responses to Day 180 RMS Preliminary Assessment Report. PIL update.