VI.2 Elements for a public summary

VI.3 Overview of disease epidemiology

Hepatitis B virus (HBV) causes infection of the liver. HBV is spread by exposure to blood which may occur through sex, by sharing drug injection equipment like needles or syringes, or from mother to infant at the time of birth, and by close household contact. Individuals with frequent exposures to blood products like healthcare workers and dialysis patients are at higher than average risk of becoming infected with HBV.

Each year there are up to 30 million new HBV infections worldwide and approximately 15,000 new infections in the European Union. HBV infection ranges in severity from a mild illness lasting a few weeks or months to a serious, lifelong illness. Acute HBV infection is a short-term illness that resolves within 6 months following infection. Chronic hepatitis B (CHB) infection is a long-term illness that occurs when the hepatitis B virus remains in a person's body for longer than 6 months. The younger a person is when he or she becomes infected with HBV, the greater the risk for developing CHB. CHB is a serious disease that can result in liver damage including cirrhosis (scarring), liver failure, liver cancer, and death.

VI.3.1 Summary of treatment benefits

The need for treatment of CHB infection is based on blood tests (serum HBV DNA levels and serum ALT and AST levels) and severity of liver disease. One way to judge the severity of liver disease is by a

liver biopsy (looking at a small sample of the liver under a microscope). Drugs that are available for the treatment of CHB include various types of interferons and 5 different drugs from a class called nucleos(t)ide analogues or NAs. Lamivudine, adefovir, entecavir, telbivudine, and tenofovir are NAs that have been approved in Europe for CHB treatment. The European Association for the Study of the Liver (EASL) recommends either entecavir or tenofovir alone as initial NA treatment for CHB infection because both drugs are potent and because it is difficult for HBV to develop resistance to these drugs. After initial treatment with drugs other than entecavir have failed due to the development of resistance, entecavir either as a single drug or in combination with another NA, may also be used depending on the specific prior drugs and the potential for cross-resistance.

The results of five clinical trials support entecavir indications.

- In 2 different studies in adult patients with compensated liver disease, 610 patients treated with entecavir were compared to 601 patients treated with lamivudine. Significantly more patients in the entecavir group had improvements in blood tests and severity of liver disease as measured by liver biopsy than patients in the lamivudine groups.

- In a single study in adult patients who were currently being treated with lamivudine and who became refractory to lamivudine treatment, 124 subjects were switched to entecavir and 116 remained on lamivudine therapy. Significantly more patients in the entecavir group had improvement in blood tests and severity of liver disease as measured by liver biopsy.

- In a single study in adult patients with decompensated liver disease, 100 patients treated with entecavir were compared to 91 patients treated with adefovir. Significantly more

patients in the entecavir group had improvements in blood tests and liver function as measured by a score called the Child-Turcotte-Pugh (CTP) score.

- In a single Phase 3 study in paediatric patients from 2 to <18 years of age with compensated liver disease, 82 patients treated with entecavir were compared to 41 patients treated with placebo. Significantly more patients in the entecavir group had improvement in both blood tests for virus in the body and immunity in controlling the virus.

Additional studies have been completed in ethnic and racial minorities and liver transplantation patients and entecavir appears to be safe and effective in these populations as well.

VI.3.2 Unknowns relating to treatment benefits

In the 4 adult studies discussed above, all patients were 16 years or older. The mean age in each of the three trials was 35, 44, and 52 years. There is limited clinical trial information in elderly patients.

The patients in these studies tended to be male, white, and Asian although upwards of 20% of participants were women. Few blacks/African Americans and persons of Hispanic descent were included in these trials. Subsequently a small trial with black and Hispanic patients was conducted and the efficacy and adverse events that were observed were no different in this population. In the paediatric study discussed above, all patients were from 2 to <18 years of age. Overall there has been no evidence that entecavir works differently or has a different side effect profile in any one group of

individuals evaluated to date. There is still not enough data to determine if entecavir is safe and effective in pregnant women and in women who are breast feeding.

VI.3.3 Summary of safety concerns Important identified risks

Risk	What is known	Preventability
Worsening of hepatitis (Exacerbation of Hepatitis)	There are two different situations where worsening of hepatitis occurs. The first situation is when entecavir is first started. About 2 % of people will have a hepatitis "flare" during which time the liver blood tests (called ALT and AST) increase. These flares are associated with a decreased amount of HBV in the blood and rarely require intervention. In the second situation, worsening of hepatitis occurs after entecavir is discontinued. Between 6 and 12% of people with CHB who are treated with ETV will have hepatitis flares that occur 17 to 24 weeks after entecavir is stopped. People may have symptoms and complications associated with worsening of hepatitis in this situation particularly if they have cirrhosis and decompensated liver disease.	Worsening of hepatitis in these situations cannot be prevented, however the condition can be monitored through blood tests (ALT, AST), and it is recommended to monitor these blood tests after entecavir is stopped. Severe hepatitis flares occurring after entecavir has been stopped can be treated by resuming entecavir therapy.

The resistance of the virus entecavir (Entecavir Resistance)	In nucleos(t)ide-naive patients, 1.2% of patient viruses developed resistance after 5 years of therapy. In patients who had received the NA lamivudine and developed lamivudine resistance before changing to entecavir, 51% of patients developed resistance after 5 years. When resistance develops, control of HBV measured in the blood (HBV DNA) is lost and this may result in progression of infection to cirrhosis, decompensated disease, liver cancer, and death.	In patients who have received prior lamivudine and in whom lamivudine no longer works due to resistance, or in patients with decompensated liver disease and lamivudine resistance, combination therapy with entecavir plus another NA that does not have cross resistance to entecavir is recommended.
Development of Human Immunodeficiency Virus (HIV) resistance in patients with both HIV and HBV infections who are not receiving HIV treatment at the same time as entecavir therapy	In general, treatment of HIV requires three active drugs to stop the virus from multiplying in the blood of infected people. When only one drug is used, HIV can become resistant to the one drug relatively quickly. Although entecavir is not used to treat HIV, it does have some activity against HIV. People with both HIV and HBV infections should be on effective HIV	Patients who are being considered for entecavir therapy should have an HIV test if their HIV status is unknown. When entecavir is used in patients with both HIV and HBV infections, effective HIV treatment should also be administered.

Risk	What is known	Preventability
(Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment)	treatment before beginning entecavir.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Development of cancer (Carcinogenicity)	During drug development, animals are exposed to drugs, sometimes at very high levels, in order to determine if the drug might be associated with the development of cancer. In mice and rats, certain benign (not cancer) and cancerous tumours occurred following these exposures. Further investigation in the animal models suggested that the tumours that developed in animals probably would not occur in humans because humans lack the pathway that is necessary to induce lung tumours seen in mice or the tumours occur at very high levels of entecavir exposure that humans would never be exposed to. The clinical studies database for entecavir was examined and there was no indication that cancers were increased in patients exposed to entecavir. It is important to understand that people who are infected with HBV are at a high risk of developing hepatocellular or liver cancer, also called HCC. In addition, 2 large studies showed that people with HBV infection have a somewhat increased risk of lymphoma and pancreatic cancer. These risks are due to the disease and are independent of entecavir exposure.

Damage to mitochondria (Mitochondrial Toxicity)	Mitochondria are sometimes referred to as the power house of individual human cells. Energy from the mitochondria is necessary to carry out all of the cell functions that support life. If the mitochondria are damaged they cannot provide all the energy that our bodies need to function properly. This can result in damage to vital organs including the liver, muscles, nerves, and pancreas. NAs as a class of drug are known to cause mitochondrial damage. One of the blood tests that become increased when mitochondria are damaged is called lactic acid. Since the condition of mitochondria cannot be easily assessed, healthcare professionals use lactic acid levels as a marker for mitochondrial damage. For a number of reasons, people with HBV infection, particularly those with decompensated liver disease; also have high levels of lactic acid. Therefore it can be difficult to determine if lactic acid is elevated due to mitochondrial damage or due the effects of CHB.

Missing information

Risk	**What is known**
Long-term Safety	Clinical trials do not typically last long enough to follow up on long-term outcomes that may occur after years of exposure to the drug being studied. For this reason, there are long-term studies with the reference product to determine if there are long-term risks associated with entecavir use. In addition. So far, these longer term studies and data monitoring activities have

Risk	What is known
	not identified additional risks associated with entecavir treatment.
Use in the Paediatric Population	Paediatric studies of entecavir did not include subjects < 2 years old, or those who were immune tolerant. Patients in these groups would generally not qualify to be treated under current treatment guidelines.
Use in Pregnancy and Lactation	In animal studies, pregnant rabbits that were treated with extremely high doses of entecavir had offspring with birth defects mainly involving the skeleton. Pregnant women were excluded from entecavir clinical trials. During these clinical trials, some women became pregnant while taking entecavir and most of these women had therapeutic abortions. Of the women who had babies, no major defects were noted. There is no evidence that use of entecavir can prevent transmission of HBV from an infected mother to her child. It is recommends that entecavir only be used in pregnant women if the benefits to the mother clearly outweigh the risks to the foetus.
Use in Elderly Patients (≥65 years of age)	Because not many elderly patients participated in entecavir clinical trials, there is limited information regarding side effects in this population. To date, safety concerns in the elderly population appear to be similar to younger patients who are taking entecavir.
Use in severe acute exacerbation of CHB	During CHB infection, there are episodes of worsening of the hepatitis followed by periods of stability. These episodes of worsening are called acute exacerbations. Stable patients, not patients with acute exacerbations of CHB, were studied in clinical trials so there is limited information regarding starting entecavir therapy during an acute exacerbation of CHB. Several years ago, a researcher wrote a paper in which he noted that patients treated with entecavir had a higher 1 year death rate than patients treated with another nucleos(t)ide analogue called lamivudine when the drugs were initiated during severe acute exacerbations of CHB.

V1.3.4 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 Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

V1.3.5 Planned post authorisation development plan

Not applicable.

V1.3.6 Summary of changes to the risk management plan over time

Not applicable.