Entecavir STADA 0.5 mg and 1 mg film-coated tablets

14.6.2016, Version V1.0

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

Entecavir Stada 0.5 mg film-coated tablets
Entecavir Stada 1 mg film-coated tablets

VI.2.1 Overview of disease epidemiology

The hepatitis B virus (HBV) disease represents a major public health concern, with more than 350 million people infected and about 1 million deaths annually. The occurrence of HBV varies widely by geographic area, ranging from 0.1-2% in low-occurrence areas such as Western Europe to 8% and more in the high-occurrence areas of South-East Asia and Sub-Saharan Africa. Following acute hepatitis B infection, approximately 5% of adults and 20-90% of children, depending on the age at infection, produce an insufficient immune response and become chronic carrier of the virus. Patients with chronic HBV are at increased risk of developing long-term complications, i.e. cirrhosis, liver failure and liver cancer. Among patients with chronic active hepatitis B, about 40% will develop cirrhosis over their lifetime at a rate of approximately 2% per year. Among patients with counterbalanced (compensated) cirrhosis, 10% per year progress to an unbalanced (decompensated) state, with a 1-year survival rate of 60%, compared with over 90% for counterbalanced cirrhosis.

VI.2.2 Summary of treatment benefits

Entecavir Stada tablets are anti-viral medicines, used to treat chronic (long term) hepatitis B virus (HBV) infection in adults.
Entecavir Stada can be used in people whose liver is damaged but still functions properly (compensated liver disease) and in people whose liver is damaged and does not function properly (decompensated liver disease).

Entecavir Stada tablets are also used to treat chronic (long term) HBV infection in children and adolescents aged 2 years to less than 18 years.
Entecavir Stada can be used in children whose liver is damaged but still functions properly (compensated liver disease).

Infection by the hepatitis B virus can lead to damage to the liver. Entecavir Stada reduces the amount of virus in your body, and improves the condition of the liver.

VI.2.3 Unknowns relating to treatment benefits

Information on long-term benefits of entecavir treatment is lacking. Further, the impact of entecavir on future treatment options in children and adolescents has not yet been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability

Worsening of hepatitis (Exacerbation of hepatitis)	Acute aggravation of liver disease (exacerbation of hepatitis) following stopping of therapy can occur, which leads to severe complications, particularly in patients with advanced liver cirrhosis. In patients treated with lamivudine or adefovir, these complications occasionally have resulted in death. During the clinical development of entecavir, symptoms associated with stopping of entecavir therapy have generally been benign. However, the frequency of severe complications following withdrawal of entecavir may be greater in the post-marketing period than during clinical studies, as a broader population of patients, including those with severe simultaneous diseases (co-morbidities), is exposed to the drug.	Patients must not stop taking entecavir without their doctor's advice. The doctor will continue monitoring blood values after treatment with entecavir for several months. Patients should inform their doctor immediately about any changes in symptoms that they notice after stopping treatment. Patients should discuss with their doctor whether their liver functions properly and, if not, what the possible effects on entecavir treatment may be.
Hepatitis B virus may become insensitive to antiviral treatment with entecavir (ETV resistance)	If the hepatitis B virus becomes insensitive to treatment with the antiviral medication entecavir (antiviral resistance), a loss of clinical effect and potential transmission of resistant HBV may happen. Patients with lamivudine resistant HBV are at higher risk of developing subsequent entecavir resistant HBV than patients not previously treated with lamivudine. Insensitivity to entecavir treatment may be associated with disease progression to cirrhosis, liver failure and liver cancer.	A doctor will advise patients on the dose that is right for them. Patients must always take the dose recommended by their doctor to ensure that the medicine is fully effective and to reduce the development of resistance to treatment. Patients must take entecavir as long as their doctor tells them.
HIV may become insensitive to treatment in patients who are also infected with HIV and only receiving entecavir but no effective medicines against HIV at the same time (Emergence of resistant HIV	Emergence of insensitivity of Human Immunodeficiency Virus (HIV) to treatment (resistance) has been observed when entecavir is used to treat chronic HBV infection in HIV/HBV co-infected patients who are not	Patients who are also infected with HIV (human immunodeficiency virus) must tell their doctor. Entecavir should not be taken to treat hepatitis B infection without taking medicines against HIV at the

in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment)	receiving effective HIV treatment at the same time. This resistance potentially limits future HIV treatment options (specifically it gives resistance to lamivudine and emtricitabine, which are part of preferred and alternative anti-HIV therapies). In HIV/HBV co-infected patients, entecavir has only been studied in patients receiving concomitant effective HIV therapy and has not been studied for use against HIV. Changes in the viruses that can lead to resistance in HIV/HBV co-infected patients receiving entecavir have been reported.	same time, as the effectiveness of future HIV treatment may be reduced.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Risk of cancer (Carcinogenicity)	Analyses of cases of cancer that have occurred during clinical studies using entecavir do not show an increase in cancer in humans over the expected rate in patients with chronic HBV or in the comparator group. The analyses may not have detected all cases of cancer because cancer development may take longer than the duration of the study. The majority of patients were observed for up to 52 weeks. Additionally, relatively rare events are difficult to assess during clinical development due to the limited number of patients.
Excess of lactic acid in the blood caused by impairment of the cell's energy production (Mitochondrial toxicity)	Entecavir belongs to a class of medicines that can impair the cell's energy production (mitochondrial toxicity) and thereby cause an excess of lactic acid in the blood (lactic acidosis). Symptoms such as nausea, vomiting and stomach pain might indicate the development of lactic acidosis. This rare but serious side effect has occasionally led to death. It occurs more often in women, obese people, during pregnancy and, specifically in case of HIV infection, in patients with a low amount of a specific immune cell in the blood (CD4).

Missing information

Risk	**What is known**

Unknown risks and benefits of long-term use (Long term safety and clinical outcomes data)	Three entecavir studies allow for long-term follow up of entecavir-treated patients, to assess potential risks of cancer and other long-term complications. Two studies (AI463049 and AI463901) were completed, but the results are not publicly available yet. The third long-term study (A1463080) is still ongoing.
Use in children and adolescents (Use in the paediatric population)	Long-term follow up of safety and efficacy has been investigated in studies AI463028 and AI463189 that have been performed by the first authorised entecavir product (originator). First results indicate that the treatment of children and adolescents is effective.
Use in pregnancy and during breast-feeding (Use in pregnancy and lactation)	It has not been demonstrated that entecavir is safe to use during pregnancy. Entecavir must not be used during pregnancy unless specifically directed by the doctor. It is important that women of childbearing age receiving treatment with entecavir use an effective method of contraception to avoid becoming pregnant. Women should not breast-feed during treatment with entecavir. Women should tell their doctor if they are breast-feeding. It is not known whether entecavir is excreted in human breast milk.
Use in elderly patients (≥ 65 years of age)	Clinical studies of entecavir did not include sufficient numbers of patients aged ≥ 65 years to determine whether they respond differently from younger subjects. Uptake into and removal from the body of entecavir does not differ by age. No dosage adjustment of entecavir based on age is required. However, entecavir is substantially eliminated from the body through the kidneys, and the risk of toxic reactions to entecavir may be greater in elderly patients since they are more likely to have decreased renal function. Dosage adjustment is recommended for patients suffering from a specific state of impaired kidney function measured as creatinine clearance < 50 mL/minute, including patients who must have their blood cleaned by dialysis.
Use in severe worsening of chronic hepatitis B (Use in severe acute exacerbation of chronic hepatitis B)	In a study by Wong et al. a higher 1-year death rate was identified with entecavir treatment compared to lamivudine treatment in a specific group of patients with spontaneous severe acute aggravation of chronic hepatitis B. No further publications have been identified that indicate a potential for increase in liver-specific death with entecavir treatment.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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

No post-authorisation studies have been imposed or are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.