Rx Prescription only

Entecavir STELLA 0.5 mg film-coated tablet

1. **Name of the medicinal product**
   Entecavir STELLA 0.5 mg film-coated tablet
2. **The signs should be noted and recommended**
   Keep out of reach of children
   Read the package insert carefully before use
3. **Composition**
   Each film-coated tablet contains:
   Entecavir (as entecavir monohydrate) ..... 0.5 mg
   Excipients q.s. ..... 1 tablet
4. **Pharmaceutical form**
   Film-coated tablet.
   White, triangle-shaped, film-coated tablet, engraved with "0.5" on one side and "E" on the other side.
5. **Indications**
   Entecavir STELLA 0.5 mg film-coated tablet is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.
   The following points should be considered when initiating therapy with Entecavir STELLA 0.5 mg film-coated tablet:
   - This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naïve and lamivudine-resistant adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease.
   - Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease.
   - Virologic, biochemical, serologic, and safety data are available for a limited number of adults with HIV/HBV co-infection who have received prior lamivudine therapy.
6. **Administration and dosage**
   Administration
   Entecavir STELLA 0.5 mg film-coated tablet should be taken orally.
   Dosage
   - *Compensated liver disease*
     Nucleoside naïve patients: The recommended dose of Entecavir STELLA is 0.5 mg orally once daily with or without food.
     Lamivudine-refractory patients (i.e., history of hepatitis B viremia while receiving lamivudine therapy or known lamivudine resistance [LVDr, commonly called YMDD] mutations): The recommended dose is 1 mg once daily. Entecavir STELLA should be taken orally, on an empty stomach (empty means at least 2 hours before and at least 2 hours after meal).
   - *Decompensated liver disease*
     The recommended dose for patients with decompensated liver disease is 1 mg once daily, which must be taken on an empty stomach (empty means at least 2 hours before and at least 2 hours after a meal).
     Special population
   - *Patients with renal impairment*
     Entecavir is predominantly eliminated by the kidney. The clearance of entecavir decreases with impaired (decreasing) creatinine clearance. Dosage adjustment of Entecavir STELLA is recommended for patients who have a creatine clearance < 50 ml/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in table 1.

Table 1. Recommended dosage of Entecavir STELLA in patients with renal impairment:

Creatinine clearance (ml/min)	**Usual dose (0.5 mg once daily)**	**Lamivudine-refractory or decompensated liver disease (1 mg once daily)**
30 - < 50	0.5 mg every 48 hours	0.5 mg once daily or 1 mg every 48 hours
10 - < 30	0.5 mg every 72 hours	1 mg every 72 hours
< 10	0.5 mg every 5 – 7 days	1 mg every 5 – 7 days
Hemodialysis or CAPD	0.5 mg every 5 – 7 days	1 mg every 5 – 7 days

   Do not split tablets.
   On hemodialysis days, administer Entecavir STELLA after hemodialysis.
   CAPD = continuous ambulatory peritoneal dialysis
   - *Patients with hepatic impairment*
     No dosage adjustment of Entecavir STELLA is required in patients with hepatic impairment.
   - *Pediatric and adolescent patients*
     The safety and efficacy of Entecavir STELLA in patients < 16 years of age have not been established.
   - *Geriatric patients*
     No dosage adjustment of Entecavir STELLA based on age is required.
7. **Contraindications**
   Hypersensitivity to the active substance or to any of the excipients of the product.
8. **Special warnings and precautions for use**
   - *Renal impairment:* Dosage adjustment is recommended for patients with renal impairment. The proposed dose modifications are based on extrapolation of limited data, and their safety and effectiveness have not been clinically evaluated. Therefore, virological response should be closely monitored.
   - *Exacerbations of hepatitis:* Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline. Among entecavir-treated patients on-treatment exacerbations had a median time of onset of 4-5 weeks. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with advanced liver disease or cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.
     Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported.
     Among entecavir-treated nucleoside naïve patients, post-treatment exacerbations had a median time to onset of 23-24 weeks, and most were reported in HBeAg negative patients. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted.
   - *Patients with decompensated liver disease:* A higher rate of serious hepatic adverse events (regardless of causality) has been observed in patients with decompensated liver disease, in particular in those with Child-Turcotte-Pugh (CTP) class C disease, compared with rates in patients with compensated liver function. Also, patients with decompensated liver disease may be at higher risk for lactic acidosis and for specific renal adverse events such as hepatorenal syndrome. Therefore, clinical and laboratory parameters should be closely monitored in this patient population.
   - *Lactic acidosis and severe hepatomegaly with steatosis:* Occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues. As entecavir is a nucleoside analogue, this risk cannot be excluded. Treatment with nucleoside analogues should be discontinued when rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology occur. Benign digestive symptoms, such as nausea, vomiting and abdominal pain, might be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate. Caution should be exercised when prescribing nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease. These patients should be followed closely.
     To differentiate between elevations in aminotransferases due to response to treatment and increases potentially related to lactic acidosis, physicians should ensure that changes in ALT are associated with improvements in other laboratory markers of chronic hepatitis B.
   - *Resistance and specific precaution for lamivudine-refractory patients:* Mutations in the HBV polymerase that encode lamivudine-resistance substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with entecavir associated resistance (ETVr). In a small percentage of lamivudine-refractory patients, ETVr substitutions at residues rtT184, rtS202 or rtM250 were present at baseline. Patients with lamivudine-resistant HBV are at higher risk of developing subsequent entecavir resistance than patients without lamivudine resistance. Virological response should be frequently monitored in the lamivudine-refractory population and appropriate resistance testing should be performed. In patients with a suboptimal virological response after 24 weeks of treatment with entecavir, a modification of treatment should be considered. When starting therapy in patients with a documented history of lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy.
     Pre-existing lamivudine-resistant HBV is associated with an increased risk for subsequent entecavir resistance regardless of the degree of liver disease; 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 lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy.
   - *Paediatric population:* Entecavir should be used in these patients only if the potential benefit justifies the potential risk to the child (e.g. resistance). Since some paediatric patients may require long-term or even lifetime management of chronic active hepatitis B, consideration should be given to the impact of entecavir on future treatment options.
   - *Liver transplant recipients:* Renal function should be carefully evaluated before and during entecavir therapy in liver transplant recipients receiving ciclosporin or tacrolimus.

- *Co-infection with hepatitis C or D:* There are no data on the efficacy of entecavir in patients co-infected with hepatitis C or D virus.
- *Human immunodeficiency virus (HIV)/HBV co-infected patients not receiving concomitant antiretroviral therapy:* Entecavir has not been evaluated in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment. Emergence 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 (HAART). Therefore, therapy with entecavir should not be used for HIV/HBV co-infected patients who are not receiving HAART. Entecavir has not been studied as a treatment for HIV infection and is not recommended for this use.
- *HIV/HBV co-infected patients receiving concomitant antiretroviral therapy*: Entecavir has been studied in adults with HIV/HBV co-infection receiving a lamivudine-containing HAART regimen. No data are available on the efficacy of entecavir in HBeAg-negative patients co-infected with HIV. There are limited data on patients co-infected with HIV who have low CD4 cell counts (< 200 cells/mm^3).

General: Patients should be advised that therapy with entecavir has not been proven to reduce the risk of transmission of HBV and therefore appropriate precautions should still be taken.

9. Pregnancy and lactation

Women of childbearing potential: Given that the potential risks to the developing foetus are unknown, women of childbearing potential should use effective contraception.

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 STELLA 0.5 mg film-coated tablet 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.

Lactation

It is unknown whether entecavir is excreted in human milk. Available toxicological data in animals have shown excretion of entecavir in milk. A risk to the infants cannot be excluded. Lactation should be discontinued during treatment with Entecavir STELLA 0.5 mg film-coated tablet.

10. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Dizziness, fatigue and somnolence are common side effects which may impair the ability to drive and use machines.

11. Interactions with other drugs

Since entecavir is predominantly eliminated by the kidney, coadministration with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of either medicinal product. Apart from lamivudine, adefovir dipivoxil and tenofovir disoproxil fumarate, the effects of coadministration of entecavir with medicinal products that are excreted renally or affect renal function have not been evaluated. Patients should be monitored closely for adverse reactions when entecavir is coadministered with such medicinal products.

No pharmacokinetic interactions between entecavir and lamivudine, adefovir or tenofovir were observed.

Entecavir is not a substrate, an inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Therefore CYP450 mediated drug interactions are unlikely to occur with entecavir.

Paediatric population

Interaction studies have only been performed in adults.

12. Adverse reactions

Summary of the safety profile

In patients with compensated liver disease, the most common adverse reactions of any severity with at least a possible relation to entecavir were headache, fatigue, dizziness and nausea.

Exacerbations of hepatitis during and after discontinuation of entecavir therapy have also been reported.

List of adverse reactions

Assessment of adverse reactions is based on experience in which patients with chronic hepatitis B infection and compensated liver disease received double-blind treatment with entecavir or lamivudine for up to 107 weeks. The safety profiles, including laboratory abnormalities, were comparable for entecavir 0.5 mg daily, entecavir 1 mg daily and lamivudine.

Adverse reactions considered at least possibly related to treatment with entecavir are listed by body system organ class. Within each group, undesirable effects are presented in order of decreasing seriousness.

- *Immune system disorders*: Rare: Anaphylactoid reaction.
- *Psychiatric disorder*: Common: Insomnia.
- *Nervous system disorders*: Common: Headache, dizziness, somnolence.
- *Gastrointestinal disorder*: Common: Vomiting, diarrhoea, nausea, dyspepsia.
- *Hepatobiliary disorders*: Common: Increased transaminases.
- *Skin and subcutaneous tissue disorders*: Uncommon: Rash, alopecia.
- *General disorders and administration site conditions*: Common: Fatigue.

Cases of lactic acidosis have been reported, often in association with hepatic decompensation, other serious medical conditions or drug exposures.

Treatment beyond 48 weeks: Continued treatment with entecavir for a median duration of 96 weeks did not reveal any new safety signals.

Description of selected adverse reactions

Laboratory test abnormalities:

Among nucleoside-naive patients, number of patients had ALT elevations > 3 times baseline and ALT elevations > 2 times baseline together with total bilirubin > 2 times upper limit of normal (ULN) and > 2 times baseline. Albumin levels < 2.5 g/dl, amylase levels > 3 times baseline, lipase levels > 3 times baseline and platelets < 50,000/mm^3 occurred in some patients.

Among lamivudine-refractory patients, number of patients had ALT elevations > 3 times baseline and ALT elevations > 2 times baseline together with total bilirubin > 2 times ULN and > 2 times baseline. Amylase levels > 3 times baseline, lipase levels > 3 times baseline and platelets < 50,000/mm^3 occurred in some patients.

Exacerbations during treatment:

In nucleoside naive patients and lamivudine-refractory patients, on treatment ALT elevations > 10 times ULN and > 2 times baseline occurred in entecavir treated patients vs lamivudine treated patients.

Among entecavir-treated patients, on-treatment ALT elevations had a median time to onset of 4-5 weeks, generally resolved with continued treatment, and, in a majority of cases, were associated with a ≥ 2 $\log_{10}$/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations after discontinuation of treatment:

- Acute exacerbations of hepatitis have been reported in patients who have discontinued anti-hepatitis B virus therapy, including therapy with entecavir. In nucleoside-naive patients, some entecavir-treated patients and lamivudine-treated patients experienced ALT elevations (> 10 times ULN and > 2 times reference [minimum of baseline or last end-of-dosing measurement]) during post-treatment follow-up. Among entecavir-treated nucleoside-naïve patients, ALT elevations had a median time to onset of 23-24 weeks, and almost of ALT elevations occurred in HBeAg negative patients. In lamivudine-refractory patients, with only limited numbers of patients being followed up, a few number of entecavir-treated patients and no lamivudine-treated patients developed ALT elevations during post-treatment follow-up.
- Entecavir treatment was discontinued if patients achieved a prespecified response. If treatment is discontinued without regard to treatment response, the rate of post-treatment ALT flares could be higher.

Paediatric population:

The safety of entecavir in paediatric patients from 2 to < 18 years of age is based on trials in patients with chronic HBV infection. These trials provide experience in number of HBeAg-positive nucleoside-treatment-naïve patients treated with entecavir for a median duration of 99 weeks. The adverse reactions observed in paediatric patients who received treatment with entecavir were consistent with those observed in adults.

Other special populations:

- *Experience in patients with decompensated liver disease:*

The safety profile of entecavir in patients with decompensated liver disease was assessed, in which patients received treatment with entecavir 1 mg/day or adefovir dipivoxil 10 mg/day. Relative to the adverse reactions noted in section *List of adverse reactions*, one additional adverse reaction [decrease in blood bicarbonate] was observed in entecavir-treated patients through week 48. The causes of death were generally liver-related, as expected in this population. Serious adverse events were generally liver-related. Patients with high baseline CTP score were at higher risk of developing serious adverse events.

- *Laboratory test abnormalities*: Through week 48 among entecavir-treated patients with decompensated liver disease, none had ALT elevations both > 10 times ULN and > 2 times baseline and few patients had ALT elevations > 2 times baseline together with total bilirubin > 2 times ULN and > 2 times baseline. Albumin levels < 2.5 g/dl, lipase levels > 3 times baseline and platelets < 50,000/mm^3 occurred in several patients.
- *Experience in patients co-infected with HIV:*

The safety profile of entecavir in a limited number of HIV/HBV co-infected patients on lamivudine-containing HAART (highly active antiretroviral therapy) regimens was similar to the safety profile in monoinfected HBV patients.

- *Gender/age:*

There was no apparent difference in the safety profile of entecavir with respect to gender or age.

13. Overdosage and treatment

There is limited experience of entecavir overdose reported in patients. Healthy people who received up to 20 mg/day for up to 14 days, and single doses up to 40 mg had no unexpected adverse reactions. If overdose occurs, the patient must be monitored for evidence of toxicity and given standard supportive treatment as necessary.

14. Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors.

ATC code: J05AF10.

Entecavir, a guanosine nucleoside analogue with activity against HBV polymerase, is efficiently phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine TP, entecavir-TP functionally inhibits the 3 activities of the viral polymerase: (1) priming of the HBV polymerase, (2) reverse transcription of the negative strand DNA from the pregenomic messenger RNA, and (3) synthesis of the positive strand HBV DNA. The entecavir-TP Ki for HBV DNA polymerase is 0.0012 µM. Entecavir-TP is a weak inhibitor of cellular DNA polymerases alpha, beta, and delta with K_i values of 18 to 40 µM. In addition, high exposures of entecavir had no relevant adverse effects on gamma polymerase or mitochondrial DNA synthesis in HepG2 cells (K_i > 160 µM).

15. Pharmacokinetic properties

- *Absorption:* Entecavir is rapidly absorbed with peak plasma concentrations occurring between 0.5-1.5 hours. The absolute bioavailability has not been determined. Based on urinary excretion of unchanged drug, the bioavailability has been estimated to be at least 70%. There is a dose-proportionate increase in C_{max} and AUC values following multiple doses ranging from 0.1-1 mg. Steady-state is achieved between 6-10 days after once daily dosing with ≈ 2 times accumulation. C_{max} and C_{min} at steady-state are 4.2 and 0.3 ng/ml, respectively, for a dose of 0.5 mg, and 8.2 and 0.5 ng/ml, respectively, for 1 mg.
  Administration of 0.5 mg entecavir with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in a minimal delay in absorption (1-1.5 hour fed vs. 0.75 hour fasted), a decrease in C_{max} of 44-46%, and a decrease in AUC of 18-20%. The lower C_{max} and AUC when taken with food is not considered to be of clinical relevance in nucleoside-naïve patients but could affect efficacy in lamivudine-refractory patients.
- *Distribution:* The estimated volume of distribution for entecavir is in excess of total body water. Protein binding to human serum protein *in vitro* is ≈ 13%.
- *Biotransformation:* Entecavir is not a substrate, inhibitor or inducer of the CYP450 enzyme system. Following administration of ^{14}C-entecavir, no oxidative or acetylated metabolites and minor amounts of the phase II metabolites, glucuronide and sulfate conjugates, were observed.
- *Elimination:* Entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady-state of about 75% of the dose. Renal clearance is independent of dose and ranges between 360-471 ml/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion. After reaching peak levels, entecavir plasma concentrations decreased in a bi-exponential manner with a terminal elimination half-life of ≈ 128-149 hours. The observed drug accumulation index is ≈ 2 times with once daily dosing, suggesting an effective accumulation half-life of about 24 hours.
- *Hepatic impairment:* Pharmacokinetic parameters in patients with moderate or severe hepatic impairment were similar to those in patients with normal hepatic function.
- *Renal impairment:* Entecavir clearance decreases with decreasing creatinine clearance. A 4 hour period of haemodialysis removed ≈ 13% of the dose, and 0.3% was removed by CAPD.
- *Post-liver transplant:* Entecavir exposure in HBV-infected liver transplant recipients on a stable dose of ciclosporin A or tacrolimus was ≈ 2 times the exposure in healthy people with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these patients.
- *Gender:* AUC was 14% higher in women than in men, due to differences in renal function and weight. After adjusting for differences in creatinine clearance and body weight there was no difference in exposure between men and women.
- *Elderly:* AUC was 29% higher in the elderly than in the young, mainly due to differences in renal function and weight. After adjusting for differences in creatinine clearance and body weight, the elderly had a 12.5% higher AUC than their counterpart. The population pharmacokinetic analysis covering patients in the age range 16-75 years did not identify age as significantly influencing entecavir pharmacokinetics.
- *Race:* The population pharmacokinetic analysis did not identify race as significantly influencing entecavir pharmacokinetics. However, conclusions can only be drawn for the Caucasian and Asian groups as there were too little data in the other categories.
- *Paediatric population:* The steady-state pharmacokinetics of entecavir were evaluated in nucleoside naïve and lamivudine-experienced HBeAg-positive paediatric population from 2 to < 18 years of age with compensated liver disease. Entecavir exposure among nucleoside naïve paediatric population receiving once daily doses of entecavir 0.015 mg/kg up to a maximum dose of 0.5 mg was similar to the exposure achieved in adults receiving once daily doses of 0.5 mg. Entecavir exposure among lamivudine-experienced paediatric population receiving once daily doses of entecavir 0.030 mg/kg up to a maximum dose of 1.0 mg was similar to the exposure achieved in adults receiving once daily doses of 1.0 mg.

16. Packaging

Blister of 10 tablets. Box of 3 blisters.

17. Storage condition, shelf-life

Do not store above 30°C.
The expiry date of this pack is printed on the box. Do not use this pack after this date.

18. Name, address of manufacturer *Date of revision: February 19th, 2020*

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Manufactured by:
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