Hepcavir®

Entecavir Monohydrate

FORMS AND PRESENTATION
Hepcavir® 0.5: Film coated tablets: Box of 30.
Hepcavir® 1: Film coated tablets: Box of 30.

COMPOSITION
Hepcavir® 0.5: Each film coated tablet contains Entecavir Monohydrate 0.5 mg.
Hepcavir® 1: Each film coated tablet contains Entecavir Monohydrate 1 mg.
Excipients: Calcium carbonate, pregelatinized starch, carmellose sodium, soy polysaccharides, citric acid monohydrate, sodium stearyl fumarate, hydroxyl propylmethylcellulose, titanium dioxide, polyethylene glycol, polysorbate (Hepcavir® 0.5), red iron oxide (Hepcavir® 1).

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors.
ATC code: J05AF10.
Mechanism of action
Entecavir monohydrate, 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:
-Priming of the HBV polymerase.
-Reverse transcription of the negative strand DNA from the pregenomic messenger RNA
-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 α, β, and δ with Ki values of 18 to 40 μM. In addition, high exposures of entecavir monohydrate had no relevant adverse effects on γ polymerase or mitochondrial DNA synthesis in HepG2 cells (Ki > 160 μM).
Antiviral activity
Entecavir monohydrate inhibited HBV DNA synthesis (50% reduction, EC50) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC50 value for entecavir monohydrate against LVDr HBV was 0.026 μM (range 0.010-0.059 μM). Recombinant viruses encoding adefovir-resistant substitutions remained fully susceptible to entecavir monohydrate.
Pharmacokinetic properties
Absorption
Entecavir monohydrate 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 Cmax 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. Cmax and Cmin 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. The tablet and oral solution were bioequivalent in healthy subjects; therefore, both forms may be used interchangeably. Administration of 0.5 mg Entecavir monohydrate 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 Cmax of 44-46%, and a decrease in AUC of 18-20%. The lower Cmax and AUC when taken with food is not considered to be of clinical relevance in nucleoside-naive patients but could affect efficacy in lamivudine-refractory patients.
Distribution
The estimated volume of distribution for Entecavir monohydrate is in excess of total body water. Protein binding to human serum protein in vitro is ≈ 13%.
Biotransformation
Entecavir monohydrate is not a substrate, inhibitor or inducer of the CYP450 enzyme system. Following administration of 14C-entecavir, no oxidative or acetylated metabolites and minor amounts of the phase II metabolites, glucuronide and sulfate conjugates, were observed.
Elimination
Entecavir monohydrate 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 monohydrate 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.

INDICATIONS
Hepcavir® is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with:
▪ compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.
▪ decompensated liver disease.
For both compensated and decompensated liver disease, this indication is based on clinical trial data in nucleoside naive patients with HBeAg positive and HBeAg negative HBV infection. With respect to patients with lamivudine-refractory hepatitis B.
Hepcavir® is also indicated for the treatment of chronic HBV infection in nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS
-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 naive 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 monohydrate 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 monohydrate resistance than patients without lamivudine-resistance. The cumulative probability of emerging genotypic entecavir resistance after 1, 2, 3, 4 and 5 years treatment in the lamivudine-refractory studies was 6%, 15%, 36%, 47% and 51%, respectively. 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 monohydrate, a modification of treatment should be considered. 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 monohydrate monotherapy.
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- Paediatric population: A lower rate of virologic response (HBV DNA < 50 IU/ml) was observed in paediatric patients with baseline HBV DNA ≥ 8.0 log10 IU/ml . 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 monohydrate therapy in liver transplant recipients receiving cyclosporine or tacrolimus.
-Co-infection with hepatitis C or D: There are no data on the efficacy of

Entecavir monohydrate in patients co-infected with hepatitis C or D virus.
-Human immunodeficiency virus (HIV)/HBV co-infected patients not receiving concomitant antiretroviral therapy: Entecavir monohydrate 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 monohydrate was used to treat chronic hepatitis B infection in patients with HIV infection not receiving highly active antiretroviral therapy (HAART). Therefore, therapy with Entecavir monohydrate should not be used for HIV/HBV co-infected patients who are not receiving HAART. Entecavir monohydrate 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 monohydrate has been studied in 68 adults with HIV/HBV co-infection receiving a lamivudine-containing HAART regimen. No data are available on the efficacy of Entecavir monohydrate 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/mm3).
-General: patients should be advised that therapy with Entecavir monohydrate has not been proven to reduce the risk of transmission of HBV and therefore appropriate precautions should still be taken.

FERTILITY, 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 monohydrate in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Entecavir monohydrate should not be used during pregnancy unless clearly necessary. There are no data on the effect of Entecavir monohydrate 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 monohydrate is excreted in human milk. Available toxicological data in animals have shown excretion of Entecavir monohydrate in milk. A risk to the infants cannot be excluded. Breast-feeding should be discontinued during treatment with Hepcavir®.

DRUG INTERACTIONS

Since Entecavir monohydrate 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 monohydrate 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 monohydrate is coadministered with such medicinal products.
No pharmacokinetic interactions between Entecavir monohydrate and lamivudine, adefovir or tenofovir were observed.
Entecavir monohydrate 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 monohydrate.

ADVERSE EFFECTS

The most common adverse reactions of any severity with at least a possible relation to Entecavir monohydrate were headache, fatigue, dizziness and nausea. Exacerbations of hepatitis during and after discontinuation of Entecavir monohydrate therapy have also been reported. Adverse reactions considered at least possibly related to treatment with Entecavir monohydrate are listed by body system organ class. Frequency is defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
-Immune system disorders: Anaphylactoid reaction (rare).
-Psychiatric disorders: Insomnia (common).
-Nervous system disorders: Headache, dizziness, somnolence (common).
-Gastrointestinal disorders: Vomiting, diarrhea, nausea, dyspepsia (common).
-Hepatobiliary disorders: Increased transaminases (common).
-Skin and subcutaneous tissue disorders: Rash, alopecia (uncommon).
-General disorders and administration site conditions: Fatigue (common).
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 monohydrate for a median duration of 96 weeks did not reveal any new safety signals.

DOSAGE AND ADMINISTRATION

Hepcavir® should be taken orally and the therapy should be initiated by a physician experienced in the management of chronic hepatitis B infection.
Posology:
For compensated liver disease:
-Nucleoside naïve patients: The recommended dose is 0.5 mg once daily, with or without food.
-Lamivudine-refractory patients (i.e. with evidence of viraemia while on lamivudine or the presence of lamivudine resistance [LVDr] mutations): The recommended dose is 1 mg once daily, which must be taken on an empty stomach (more than 2 hours before or more than 2 hours after a meal).
In the presence of LVDr mutations, 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.
For 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 (more than 2 hours before or more than 2 hours after a meal).
Duration of therapy: The optimal duration of treatment is unknown. Treatment discontinuation may be considered as follows:
-In HBeAg positive patients, treatment should be administered at least until HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection on two consecutive serum samples at least 3-6 months apart) or until HBs seroconversion or there is loss of efficacy.
-In HBeAg negative patients, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.
In patients with decompensated liver disease or cirrhosis, treatment cessation is not recommended.
Elderly: No dosage adjustment based on age is required. The dose should be adjusted according to the patient's renal function.
Gender and race: No dosage adjustment based on gender or race is required.
Renal impairment: The clearance of Hepcavir® decreases with decreasing creatinine clearance. Dose adjustment is recommended for patients with creatinine clearance < 50 ml/min, including those on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A reduction of the daily dose using Hepcavir® oral solution, as detailed in the below table, is recommended. As an alternative, in case the oral solution is not available, the dose can be adjusted by increasing the dosage interval, also shown in the table. 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.

	Hepcavir® dosage	
Creatinine clearance (ml/min)	Nucleoside naïve patients	Lamivudine-refractory or decompensated liver disease
≥50	0.5 mg once daily	1mg once daily
30 - 49	0.25 mg once daily Or 0.5 mg every 48 hours	0.5mg once daily
10 - 29	0.15 mg once daily Or 0.5 mg every 72 hours	0.3 mg once daily Or 0.5 mg every 48 hours
<10 Haemodialysis or CAPD**	0.05 mg once daily Or 0.5 mg every 5-7 days	0.1 mg once daily Or 0.5 mg every 72 hours

** on haemodialysis days, administer Hepcavir® after haemodialysis.
Hepatic impairment: No dose adjustment is required in patients with hepatic impairment.
Paediatric population: For appropriate dosing in the paediatric population, Hepcavir® 0.5 film-coated tablets are available.
The decision to treat paediatric patients should be based on careful consideration of individual patient needs and with reference to current paediatric treatment guidelines including the value of baseline histological information. The benefits of long-term virologic suppression with continued therapy must be weighed against the risk of prolonged treatment, including the emergence of resistant hepatitis B virus.
Serum ALT should be persistently elevated for at least 6 months prior to treatment of paediatric patients with compensated liver disease due to HBeAg positive chronic hepatitis B; and for at least 12 months in patients with HBeAg negative disease.
Paediatric patients with body weight of at least 32.6 kg, should be administered a daily dose of one 0.5 mg tablet, with or without food.
Method of administration:
Hepcavir® should be taken orally.

OVERDOSAGE

There is limited experience of Entecavir monohydrate overdose reported in patients. Healthy subjects 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.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: October 2020.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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