

HEBECAVIR

FILM COATED TABLET 0.5 MG

Active Ingredient:

Each film coated tablet contains:

Entecavir Monohydrate 0.5 mg

Pharmacodynamics:

Mechanism of action: 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 K_i for HBV DNA polymerase is 0.0012 μM . Entecavir-TP is a weak inhibitor of cellular DNA polymerases α , β , and δ with K_i values of 18 to 40 μM . In addition, high exposures of entecavir had no relevant adverse effects on γ polymerase or mitochondrial DNA synthesis in HepG2 cells ($K_i > 160 \mu\text{M}$).

Antiviral activity: Entecavir 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 against LVD_r HBV (rtL180M and rtM204V) was 0.026 μM (range 0.010-0.059 μM). Recombinant viruses encoding adefovir-resistant substitutions at either rtN236T or rtA181V remained fully susceptible to entecavir.

An analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical HIV-1 isolates using a variety of cells and assay conditions yielded EC₅₀ values ranging from 0.026 to $> 10 \mu\text{M}$; the lower EC₅₀ values were observed when decreased levels of virus were used in the assay. In cell culture, entecavir selected for an M184I substitution at micromolar concentrations, confirming inhibitory pressure at high entecavir concentrations. HIV variants containing the M184V substitution showed loss of susceptibility to entecavir.

In HBV combination assays in cell culture, abacavir, didanosine, lamivudine, stavudine, tenofovir or zidovudine were not antagonistic to the anti-HBV activity of entecavir over a wide range of concentrations. In HIV antiviral assays, entecavir at micromolar concentrations was not antagonistic to the anti-HIV activity in cell culture of these six NRTIs or emtricitabine.

Resistance in cell culture: Relative to wild-type HBV, LVD_r viruses containing rtM204V and rtL180M substitutions within the reverse transcriptase exhibit 8-fold decreased susceptibility to entecavir. Incorporation of additional ETV_r amino acid changes rtT184, rtS202 or rtM250 decreases entecavir susceptibility in cell culture. Substitutions observed in clinical isolates (rtT184A, C, F, G, I, L, M or S; rtS202 C, G or I; and/or rtM250I, L or V) further decreased entecavir susceptibility 16- to 741-fold relative to wild-type virus. Lamivudine-resistant strains harboring rtL180M plus rtM204V in combination with amino acid substitution rtA181C conferred 16- to 122-fold reductions in entecavir phenotypic susceptibility. The ETV_r substitutions at residues rtT184, rtS202 and rtM250 alone have only a modest effect on entecavir susceptibility, and have not been observed in the absence of LVD_r substitutions in more than 1000 patient samples sequenced. Resistance is mediated by reduced inhibitor binding to the altered HBV reverse transcriptase, and resistant HBV exhibits reduced replication capacity in cell culture.

Pharmacokinetics:

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. The tablet and oral solution were bioequivalent in healthy subjects; therefore, both forms may be used interchangeably.

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 $\approx 13\%$.

Biotransformation: Entecavir 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 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 $\approx$ 128–149 hours. The observed drug accumulation index is $\approx$ 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 $\approx$ 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 cyclosporine A or tacrolimus ($n = 9$) was $\approx$ 2 times the exposure in healthy subjects 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 male and female subjects.

Elderly: The effect of age on the pharmacokinetics of entecavir was evaluated comparing elderly subjects in the age range 65–83 years (mean age females 69 years, males 74 years) with young subjects in the age range 20–40 years (mean age females 29 years, males 25 years). AUC was 29% higher in elderly than in young subjects, mainly due to differences in renal function and weight. After adjusting for differences in creatinine clearance and body weight, elderly subjects had a 12.5% higher AUC than young subjects. 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 few subjects in the other categories.

Paediatric population: Entecavir exposure among nucleoside naïve subjects 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 subjects 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.

Indication:

HEBECAVIR (entecavir) 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 HEBECAVIR:

- 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 adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy.

Recommended Dose:

Compensated liver disease

Nucleoside-naïve patients: the recommended dose in adults is 0.5 mg once daily, with or without food.

Lamivudine-refractory patients (i.e. history of hepatitis B viremia while receiving lamivudine therapy or known lamivudine resistance [LVD_r, commonly called YMDD] mutations): the recommended dose is 1 mg once daily, which must be taken orally on an empty stomach (empty means at least 2 hours before and at least 2 hours after a 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 Populations:

Patients with Renal Impairment

Entecavir is predominantly eliminated by the kidney. The clearance of entecavir decreases with impaired (decreasing) creatinine clearance.

Dosage adjustment of HEBECAVIR is recommended for patients who have a creatinine clearance <50 mL/min, including those on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 1.

Table 1: Recommended Dosage of HEBECAVIR in Patients with Renal Impairment^a

Creatinine Clearance (mL/min)	Usual Dose (0.5mg once daily)	Lamivudine-Refractory or Decompensated Liver Disease (1mg once daily)
30 - <50	0.5mg every 48 hours	0.5mg once daily OR 1mg every 48 hours
10 - <30	0.5mg every 72 hours	1mg every 72 hours
<10	0.5mg every 5-7 days	1mg every 5-7 days
Haemodialysis ^b or CAPD	0.5mg every 5-7 days	1mg every 5-7 days

^a: Do not split tablets.

^b: On haemodialysis days, administer HEBECAVIR after haemodialysis.

CAPD=continuous ambulatory peritoneal dialysis.

Patient with hepatic impairment

No dosage adjustment of HEBECAVIR is required for patients with hepatic impairment.

Pediatric and adolescent patients

The safety and efficacy of HEBECAVIR in patients <16 years of age have not been established.

Geriatric patients

No dosage adjustment of HEBECAVIR based on age is required.

Route of Administration:

Oral administration. HEBECAVIR should be taken orally.

Contraindications:

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

Warning and Precautions:

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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. 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, 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.

9. 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.
10. Paediatric population: A lower rate of virologic response (HBV DNA < 50 IU/ml) was observed in paediatric patients with baseline HBV DNA $\geq 8.0 \log_{10}$ 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.
11. Liver transplant recipients: Renal function should be carefully evaluated before and during entecavir therapy in liver transplant recipients receiving cyclosporine or tacrolimus.
12. 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.
13. 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.
14. HIV/HBV co-infected patients receiving concomitant antiretroviral therapy: Entecavir 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 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).
15. General: Patient 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.
16. This medicinal product contains lactose.
17. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with Other Medicaments:

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.

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. HEBECAVIR 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.

Breast-feeding: 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. Breast-feeding should be discontinued during treatment with HEBECAVIR.

Fertility: Toxicology studies in animals administered entecavir have shown no evidence of impaired fertility.

Side Effects:

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.

Tabulated List of Adverse Reactions

Adverse reactions considered at least possibly related to treatment with entecavir are listed by body system organ class. Frequency is defined as very common, common, uncommon, rare. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Body system organ class	Frequency	Undesirable effects
Immune system disorders	Rare	anaphylactoid reaction
Psychiatric disorders	Common	insomnia
Nervous system disorders	Common	headache, dizziness, somnolence
Gastrointestinal disorders	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 (see section warning and precaution).

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

Effects on Ability to Drive and Use Machine:

No studies on the effect 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.

Instruction for Use:

HEBECAVIR should be taken orally.

Symptoms and Treatment of Overdose:

There is limited experience of entecavir 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 Condition:

Store at temperature below 30°C. Protect from light and moisture.

Shelf Life:

3 years from the date of manufacture

Product Description & Packing(s):

A white color film coated triangular tablet, one side impressed with '5', the other side impressed with 'Y'.



10's x 3, 10's x 10.



Manufacturer and Product Registration Holder:
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