

Encavid Tablets 0.5 mg

DESCRIPTION

White colored, circular, biconvex, film coated tablets which are plain on both sides.

COMPOSITION

Each film-coated tablet contains Entecavir monohydrate 0.54mg eq to Entecavir 0.5mg.

ACTIONS AND PHARMACOLOGY

Entecavir is 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 α, β, and δ with Ki 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 (Ki > 160 µM).

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 approximately 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.

Distribution

The estimated volume of distribution for entecavir is in excess of total body water. Protein binding to human serum protein *in vitro* is approximately 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 biexponential manner with a terminal elimination half-life of approximately 128-149 hours. The observed drug accumulation index is approximately 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 approximately 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 was approximately 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

After adjusting for differences in creatinine clearance and body weight, no difference in exposure between male and female subjects was observed.

Elderly

The population pharmacokinetic analysis covering patients in the age range 16-75 years did not identify age as significantly influencing entecavir pharmacokinetics.

Paediatric population

Entecavir exposure among nucleoside naïve HBeAg-positive paediatric patients from 2 to <18 years of age with compensated liver disease 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.

INDICATIONS

Encavid (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 Encavid:

- a) This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment- naïve and

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lamivudine-resistant adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease.

- b) Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease.
- c) 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.

CONTRAINDICATIONS

Entecavir is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND 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 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. 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.

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 cyclosporine 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

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).

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.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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. The potential risk for humans is unknown. Encavid Tablets 0.5mg 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. A risk to the infants cannot be excluded. Breast-feeding should be discontinued during treatment with Encavid Tablets 0.5mg.

Fertility

No evidence of impaired fertility has been shown.

DRUG INTERACTIONS

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 co-administered 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.

MAIN SIDE/ ADVERSE EFFECTS

Summary of 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

Adverse reactions considered at least possibly related to treatment with entecavir are listed by body system organ class.

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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.

SYMPTOMS OF OVERDOSE AND TREATMENT

There is limited experience of Entecavir overdose reported in patients. If overdose occur, the patient must be monitored for evidence of toxicity and given standard supportive treatment as necessary.

DOSAGE AND ADMINISTRATION

For oral use.

Compensated liver disease

Nucleoside naive patients: The recommended dose of Encavid Tablets 0.5mg is 0.5mg 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 [LVD_r, commonly called YMDD] mutations): The recommended dose is 1mg once daily. Encavid Tablets 0.5mg should 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).

Renal impairment

Entecavir is predominantly eliminated by the kidney. The clearance of entecavir decreases with impaired (decreasing) creatinine clearance. Dosage adjustment of Encavid Tablets 0.5mg is recommended for patients who have a creatinine clearance <50 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 1.

Table 1: Recommended Dosage of Encavid Tablets 0.5mg in Patients with Renal Impairment^a:

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 ^b or CAPD	0.5 mg every 5-7 days	1 mg every 5-7 days

^a Do not split tablets.

^b On hemodialysis days, administer Encavid Tablets 0.5mg after hemodialysis.

CAPD=continuous ambulatory peritoneal dialysis.

Hepatic impairment

No dosage adjustment of Encavid Tablets 0.5mg is required in patients with hepatic impairment.

Pediatric and adolescent patients

The safety and efficacy of Encavid Tablets 0.5mg in patients <16 years of age have not been established.

Elderly

No dosage adjustment of Encavid Tablets 0.5mg based on age is required.

Note: The information given here is limited. For further information, kindly consult your doctor or pharmacist.

Storage: Store below 30°C. Protect from light.

Presentation/Packing: Blister pack of 3x10's

Product Registration Holder: **HOVID Pharmacy Sdn.Bhd.**

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