Proposed Artwork

hovid

Hovid Entecavir Tablets

VIENT03-var1 (MY)

DESCRIPTION

Hovid Entecavir Tablets 0.5 mg
White triangular shaped film-coated tablets debossed 'A' on one side and '88' on the other side.

Hovid Entecavir Tablets 1 mg
Pink triangular shaped film-coated tablets debossed 'A' on one side and '89' on other side.

COMPOSITION

Hovid Entecavir Tablets 0.5 mg
Each tablet contains 0.5 mg Entecavir.

Hovid Entecavir Tablets 1 mg
Each tablet contains 1 mg Entecavir.

PHARMACODYNAMICS

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 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 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 ^{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 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 paediatric patients 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 patients 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.

INDICATIONS

Hovid 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 indication is based on the reported histologic, virologic, biochemical and serologic response in:

a) Nucleoside-treatment naive and lamivudine-resistant adult patient with HBeAg positive or HBeAg negative HBV infection with compensated liver disease.
b) Adult patient with chronic HBV infection and decompensated liver disease.
c) Adult patient with HIV/HBV co-infection who have received prior lamivudine therapy.

CONTRAINDICATIONS

Hovid 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.

Exacerbation 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 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 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
Hovid 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.

9 8 8

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 anti-retroviral therapy (HAART). Therefore, therapy with Hovid 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/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.

Lactose
This medicinal product contains 120.5 mg of lactose in each 0.5 mg daily dose or 241 mg of lactose in each 1 mg daily dose.

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

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.

PREGNANCY AND LACTATION
Women of childbearing potential
Women of childbearing potential should use effective contraception if administer with Hovid Entecavir.

Pregnancy
Hovid Entecavir should not be used during pregnancy unless clearly necessary.

Lactation
It is not known whether Hovid Entecavir is excreted in breast milk. Breast-feeding should be discontinued during treatment with Hovid Entecavir.

DRUG INTERACTIONS
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.

MAIN SIDE/ ADVERSE EFFECTS
Immune System Disorders
Rare: Anaphylactoid reaction

Psychiatric Disorders
Common: Insonmia

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.

OVERDOSE AND TREATMENT
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 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 naïve patients: the recommended dose 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 [LVDr, commonly called YMDD mutation): The recommended dose is 1 mg once daily, which 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).

Duration of therapy
The optimal duration of treatment is unknown. Treatment discontinuation may be considered as follows:
- In HBeAg positive adult patients, treatment should be administered at least until 12 months after achieving 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 adult 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.

Paediatric population
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.

Duration of therapy for paediatric patients
The optimal duration of treatment is unknown. In accordance with current paediatric practice guidelines, treatment discontinuation may be considered as follows:
- In HBeAg positive paediatric patients, treatment should be administered for at least 12 months after achieving undetectable HBV DNA and HBeAg seroconversion (HBeAg loss and anti-HBe detection on two consecutive serum samples at least 3-6 months apart) or until HBs seroconversion or there is loss of efficacy. Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation.
- In HBeAg negative paediatric patients, treatment should be administered until HBs seroconversion or there is evidence of loss of efficacy.

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 entecavir 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). The adjusted dose is shown in table below. 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.

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

*On haemodialysis days, administer Hovid Entecavir after haemodialysis.

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment.

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

Storage: Store below 30°C.
Store in the original carton.

Presentation/Packing: Blister pack of 3x10's

Product Registration Holder: **HOVID Bhd.**
121, Jalan Tunku Abdul Rahman (Jalan Kuala Kangsar),
30010 Ipoh, Perak, Malaysia.

Manufactured by : Cohance Lifesciences Limited,
Plot No. A-19/C, A-23A & A-23B, Road No. 18,
IDA Nacharam, Nacharam Village, Uppal Mandal,
Medchal, Malkajgiri District, 500 076, Telangana, India.

Information date: June 2023