For the Use of a Registered Medical Practitioner Only

PRESCRIBING INFORMATION

Enteca Tablets 0.5mg and 1mg
(Entecavir Tablets)

DESCRIPTION

Enteca Tablets (entecavir) is a guanosine nucleoside analogue with potent and selective activity against hepatitis B virus (HBV).

Enteca Tablets is available for oral administration as film-coated tablets in strength of 0.5 mg and 1mg of entecavir.

INDICATIONS

Enteca 0.5/1 mg tablets are indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum alanine aminotransferases (ALT or AST) or histological active disease.

This indication is based on the reported histologic, virologic, biochemical, and serological response in nucleoside-treatment naive and lamivudine-resistant adult patient with HBeAg positive and HBeAg negative HBV infection with compensated liver disease and on more limited data in adult patient with HIV/HBV co-infection who have received prior lamivudine therapy.

DOSAGE AND ADMINISTRATION

Recommended dosage

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 vireamia while receiving lamivudine therapy or known lamivudine resistance [LVDr, commonly called YMDD] mutations): the recommended dose is 1 mg once daily. Entecavir be taken orally, 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 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 below.

Recommended Dosage of Entecavir in Patients with Renal Impairment: Schedule-Based Method		
Creatinine Clearance (ml/min)	**Usual Dose (0.5 mg once daily)**	**Lamivudine-refractory (1 mg once daily)**
30 – <50	0.5 mg every 48 hours	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

*on haemodialysis days, administer entecavir after haemodialysis.

CAPD- continuous ambulatory peritoneal dialysis.

Patients with hepatic impairment

No dosage adjustment of entecavir is required in patients with hepatic impairment.

Pediatric and adolescent population

The safety and efficacy of entecavir in children below 16 years of age have not been established.

Geriatric

No dosage adjustment of entecavir based on age is required.

CONTRAINDICATIONS

Entacavir is contraindicated in patients with previously demonstrated hypersensitivity to entecavir or any component of the product.

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 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 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.

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. Enteca 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 Enteca.

Fertility

No evidence of impaired fertility has been shown

Pediatric Use

Safety and effectiveness of Enteca Tablets in pediatric patients below the age of 16 years have not been established.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Medicinal Products

Since entecavir is predominantly eliminated by the kidney,coadministration of Enteca Tablets with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of either medicinal product. Coadministration of Enteca Tablets with either lamivudine, adefovir dipivoxil or tenofovir disoproxil fumarate resulted in no significant drug interactions. The effects of coadministration of Enteca Tablets with other medicinal products that are excreted renally or affect renal function have not been evaluated. Patients should be monitored closely for adverse events when Enteca Tablets 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

Food

Administration of entecavir with food decreased absorption by 18-20%.

UNDESIRABLE EFFECTS

Nucleoside naïve patients

Adverse reactions of moderate intensity or greater and considered at least possibly related to treatment with Enteca Tablets are listed by body system organ class.

Psychiatric disorders:
Uncommon: insomnia

Nervous system disorders:
Common: headache
Uncommon: dizziness, somnolence

Gastrointestinal disorders:
Uncommon: nausea, diarrhea, dyspepsia, vomiting

General disorders and administration site conditions:
Common: fatigue

Lamivudine-refractory Patients

Adverse reactions of moderate intensity or greater and considered at least possibly related to treatment with Enteca Tablets are listed by body system organ class.

Nervous system disorders:
Common: headache

Gastrointestinal disorders:
Common: diarrhea, dyspepsia

General disorders and administration site conditions:
Common: fatigue

Exacerbations of Hepatitis after Discontinuation of Treatment

Acute exacerbations of hepatitis have been reported in patients who have discontinued anti-HBV therapy, including therapy with Enteca Tablets.

Patients Co-infected with HIV

Enteca Tablets has not been evaluated in HIV/HBV co-infected patients who are not concurrently receiving effective IV treatment.

Postmarketing Experience

Adverse Reactions from Postmarketing Spontaneous Reports

The following events have been identified during post-approval use of Enteca Tablets. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Immune system disorders: Anaphylactoid reaction.
Metabolism and nutrition disorders: Lactic acidosis has been reported, often in association with hepatic decompensation, other serious medical conditions, or drug exposures.
Patients with decompensated cirrhosis may be at higher risk for lactic acidosis.
Hepatobiliary disorders: Increased transaminases.
Skin and subcutaneous tissue disorders: Alopecia, rash.

OVERDOSAGE

There is no experience of Enteca Tablets overdose reported in patients. If overdose occurs, the patient must be monitored for evidence of toxicity and given standard supportive treatment as necessary.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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 (Ki > 160 μM).

Pharmacokinetics

Absorption

In healthy subjects, entecavir was rapidly absorbed with peak plasma concentrations occurring between 0.5 and 1.5 hours. There was a dose-proportionate increase in peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values following multiple doses ranging from 0.1 to 1 mg. Steady-state was achieved

after 6-10 days of once-daily dosing with approximately 2-fold accumulation. C_{max} and trough plasma concentration (C_{trough}) at steady-state were 4.2 and 0.3 ng/mL, respectively, for a 0.5-mg dose, and 8.2 and 0.5 ng/mL, respectively, for a 1-mg dose.

Distribution

The estimated volume of distribution for entecavir was in excess of total body water, suggesting that it has good penetration into tissues. Protein binding to human serum protein *in vitro* was approximately 13%.

Metabolism and elimination

Entecavir is not a substrate, inhibitor, or inducer of the CYP450 enzyme system. Following administration of ^{14}C-entecavir in humans and rats, no oxidative or acetylated metabolites and minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed.

Entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady-state ranging from 62% to 73% of the dose. Renal clearance is independent of dose and ranges between 360 and 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

Special Populations

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 up to maximum dose of 0.5mg was similar to the expose achieving once daily doses at 0.5mg

PHARMACEUTICAL PROPERTIES

List of Excipients

Lactose, povidone, crospovidone, microcrystalline cellulose, magnesium stearate, opadry 13B84610 pink, opadry 13B58802 white, purified water

Shelf Life

36 months.

Store below 30ºC, protected from light and moisture.

Special Precautions for Storage

Enteca Tablets should be stored in the original package at temperatures not above 30°C.

Nature and Contents of Container

Enteca 0.5 mg: White to off white coloured, caplet film coated tablet.

Enteca 1 mg: Light pink coloured, caplet film coated tablet.

They are available in aluminum blister strips of 30’s in a carton.

Manufacturer

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