(L)297mm

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pharmaniaga®

BENAVIR 0.5MG

entecavir

Benavir Film-Coated Tablet 0.5mg

COMPOSITION
Benavir is available for oral administration as film-coated tablets in strength of 0.5 mg of entecavir.

Each film-coated tablet contains 0.532 mg of entecavir monohydrate equivalence to 0.5 mg of entecavir.

DESCRIPTION
White, triangular shaped film-coated tablet with Pharmaniaga icon on one side and plain on the other.

PHARMACODYNAMICS
Pharmacotherapeutic group: antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors
ATC code: J05AF10

Mechanism of Action
Entecavir is a guanosine nucleoside analogue with potent and selective activity against Hepatitis B Virus (HBV) polymerase. It is phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. Intracellular TP levels are directly related to extracellular entecavir concentrations, with no significant accumulation beyond initial plateau levels. By competing with the natural substrate deoxyguanosine-TP, entecavir-TP inhibits all 3 functional activities of the viral polymerase: (1) priming of the HBV polymerase, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand HBV DNA. The entecavir-TP Ki for HBV DNA polymerase is 1.2 nM. 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-TP and entecavir had no relevant adverse effects on γ polymerase (Ki >160 μM) or mitochondrial DNA synthesis in HepG2 cells.

Antiviral activity
Entecavir inhibited HBV DNA synthesis (50% reduction, EC_{50}) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC_{50} value for entecavir against lamivudine-resistant HBV (rtM204V, rtL180M) 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.

EC_{50} of entecavir against laboratory and clinical HIV-1 isolates in a variety of cells and assay conditions ranged from 0.026 to >10 μM; the lower EC_{50} values were observed in decreased levels of virus 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.

PHARMACOKINETICS

Absorption
Entecavir is rapidly absorbed with peak plasma concentrations occurring between 0.5 and 1.5 hours. The bioavailability has been estimated to be at least 70% based on urinary excretion of unchanged drug. There is a dose-proportionate increase in (C_{max}) and (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 (Cmin) 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.

Oral administration of entecavir 0.5 mg 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 (1.0-1.5 hours fed vs. 0.75 hour fasted), a decrease in C_{max} 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 is in excess of total body water. Protein binding to human serum protein in vitro is ≈ 13%.

Biotransformation
Entecavir is not a substrate, inhibitor or inducer of the CYP450 enzyme system. Based on the available data, following administration of ^{14}C-entecavir, no oxidative or acetylated metabolites and minor amounts of the phase II metabolites, glucuronide and sulfate conjugates readings were documented.

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 ≈ 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.

Special Populations
Patients with renal impairment
Entecavir clearance decreases with decreasing creatinine clearance. A 4 hour period of haemodialysis removed ≈ 13% of the dose, and 0.3% was removed by CAPD.

Patients with hepatic impairment
Pharmacokinetic parameters of entecavir in patients with hepatic impairment were similar to those in patients with normal hepatic function.

Gender
There was no differences in exposure (AUC) between male and female gender.

Race
The population pharmacokinetic analysis did not identify race as significantly influencing entecavir pharmacokinetics.

Liver transplant recipients
HBV-infected liver transplant recipients exhibit increased entecavir exposure due to altered renal function.

Elderly
Pharmacokinetic profile of entecavir does not differ by age.

INDICATIONS
Benavir Tablet 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 Benavir Tablet:
• 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 DOSAGE

Compensated liver disease
Nucleoside naive patients: The recommended dose of Benavir Tablet is 0.5 mg 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 [LVDr, commonly called YMDD] mutations. The recommended dose is 1 mg once daily. Benavir Tablet 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 adult 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 Benavir Tablet 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 Benavir Tablet 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 Benavir Tablet after hemodialysis.
CAPD=continuous ambulatory peritoneal dialysis.

Patients with hepatic impairment
No dosage adjustment of Benavir Tablet is required in patients with hepatic impairment.

Pediatric and adolescent patients
The safety and efficacy of Benavir Tablet in patients <16 years of age have not been established.

Geriatric patients
No dosage adjustment of Benavir Tablet based on age is required.

ROUTE OF ADMINISTRATION
Oral.

CONTRAINDICATIONS
Benavir Tablet is contraindicated in patients with previously demonstrated hypersensitivity to entecavir or any component of the product

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 (Drug-class specific Warnings and Precautions)
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.

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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 23-24weeks, 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.

Lactic acidosis and severe hepatomegaly with steatosis (Drug-class specific Warnings and Precautions)
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.

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.

Liver transplant recipients
There is limited data are available on the safety and efficacy of Benavir Tablet in liver transplant recipients. The frequency and nature of adverse events are consistent with those expected in patients who have received a liver transplant and the known safety profile of Benavir Tablet. Renal function should be carefully evaluated before and during entecavir therapy in liver transplant recipients receiving an immunosuppressant that may affect renal function, such as 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
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).

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 120.468 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.

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
There are no data in the use of Benavir Tablet in paediatric population.

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

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. Published animal data have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Benavir Tablet 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
Published animal data reports that entecavir is excreted in the milk of rats. 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 Benavir Tablet.

ADVERSE REACTIONS

Adverse Reaction	Frequency
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

Exacerbations of hepatitis during and after discontinuation of entecavir therapy have also been reported

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 entecavir for a median duration of 96 weeks did not reveal any new safety signals.

OVERDOSE AND TREATMENT
There is no 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 events. If overdose occurs, the patient must be monitored for evidence of toxicity and given standard supportive treatment as necessary.

STORAGE CONDITIONS
Do not store above 30°C. Store in the original carton.

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

DOSAGE FORMS AND PACKAGING AVAILABLE
In boxes of 30 tablets (3 blister x 10 tablets).

PRODUCT REGISTRATION HOLDER/ MANUFACTURER:
PHARMANIAGA MANUFACTURING BERHAD (198001006232)
No.11A, Jalan P/1, Kawasan Perusahaan Bangi,
43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia

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