For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

Zentair 0.5 mg & 1 mg USP Film Coated Tablets
Entecavir 0.5 mg & 1 mg

COMPOSITION

Zentair 0.5 mg
Each film coated tablet contains:
Entecavir monohydrate BP/ Ph.Eur
Equivalent to Entecavir…….0.5 mg
Colour: Titanium Dioxide

Zentair 1 mg
Each film coated tablet contains:
Entecavir monohydrate BP/ Ph.Eur
Equivalent to Entecavir……1 mg
Colour: Titanium Dioxide & Red oxide of Iron

DOSAGE FORM
Film coated tablet

PRODUCT DESCRIPTION

Zentair 0.5 mg
White to off-white, triangular shaped biconvex, film coated tablet debossed with 'E' on one side and plain on other side.

Zentair 1 mg
Pink coloured, triangular shaped biconvex, film coated tablet debossed with "E" on one side and "1" on other side.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group
Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors

ATC code
J05AF10

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 μM).

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 LVDr 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 EC_{50} values ranging from 0.026 to > 10 μM; the lower EC_{50} 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, LVDr viruses containing rtM204V and rtL180M substitutions within the reverse transcriptase exhibit 8-fold decreased susceptibility to entecavir. Incorporation of additional ETVr 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 ETVr 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 LVDr 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 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.

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%.

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. At concentrations approximately 10,000-fold higher than those obtained in humans, entecavir inhibited none of the major human CYP450 enzymes 1A2, 2C9, 2C19, 2D6, 3A4, 2B6, and 2E1. At concentrations approximately 340-fold higher than those observed in humans, entecavir did not induce the human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5, and 2B6.

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-fold with once-daily dosing, suggesting an effective accumulation half-life of about 24 hours.

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.

Special Populations

Patients with renal impairment
Dosage adjustment is recommended for patients who have a creatinine clearance <50 mL/min.

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

Geriatric
The pharmacokinetic profile of entecavir does not differ by age.

Gender/Race
The pharmacokinetic profile of entecavir does not differ by gender or race.

Liver transplant recipients
Altered renal function contributed to the increase in entecavir exposure in HBV-infected liver transplant patients.

INDICATIONS

Zentair 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 Zentair:

- 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.

DOSAGE AND METHOD OF ADMINISTRATION

Compensated liver disease

Nucleoside-naïve patients: The recommended dose of Zentair 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. Zentair 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).

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 entecavir 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 entecavir 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 Entecavir after hemodialysis.

CAPD=continuous ambulatory peritoneal dialysis.

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

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

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

Method of administration
For oral use only

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Drug-class-specific

Lactic acidosis/hepatomegaly with steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.

Exacerbations of hepatitis after discontinuation of treatment
Acute exacerbation of hepatitis has been reported in patients who have discontinued HBV therapy, including therapy with entecavir.

The majority of post-treatment exacerbations appear to be self-limited. However, severe exacerbations, including fatalities, may occur. The causal relationship of these events to discontinuation of therapy is unknown. Hepatic function should be monitored at repeated intervals after discontinuation of therapy. If appropriate, resumption of HBV therapy may be warranted.

Product-specific

Co-infection with HIV
Entecavir has not been evaluated in patients who are co-infected with human immunodeficiency virus (HIV) and HBV and are not concurrently receiving effective HIV treatment. There is a potential for the development of HIV resistance if entecavir is used to treat chronic hepatitis B infection in patients with untreated HIV infection. Therefore, therapy with entecavir is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART). Entecavir has not been studied as a treatment for HIV infection and is not recommended for this use.

Patients with renal impairment
Dosage adjustment of entecavir is recommended for patients with renal impairment.

Liver transplant recipients
Limited data are available on the safety and efficacy of entecavir in liver transplant recipients. Renal function should be carefully monitored before and during entecavir therapy in liver transplant recipients receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus.

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.

Patient information
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.

DRUG INTERACTIONS

Medicinal products
Since entecavir is predominantly eliminated by the kidney, coadministration of entecavir with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of either medicinal product. Coadministration of entecavir with either lamivudine, adefovir dipivoxil or tenofovir disoproxil fumarate resulted in no significant drug interactions. The effects of coadministration of entecavir 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 entecavir is coadministered with such medicinal products.

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

FERTILITY, PREGNANCY AND LACTATION

There are no adequate and well-controlled studies in pregnant women. Zentair should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are no data on the effect of entecavir on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.

It is not known whether entecavir is excreted in human milk. Mothers should be instructed not to breast-feed if they are taking Zentair.

UNDESIRABLE EFFECTS

Summary of the safety profile
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.

System Organ Class	Frequency	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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

OVERDOSE

There is limited experience of entecavir overdose reported. In healthy people 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.

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.

INCOMPATIBILITIES

Not applicable

STORAGE AND HANDLING INSTRUCTIONS

Store below 30°C. Preserve in tight containers.

SHELF LIFE

24 months

PACKAGING INFORMATION

Carton containing 3 blister strips of 10 tablets each.

PRODUCT REGISTRATION HOLDER

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DATE OF REVISION

February 2023