For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Entecavir Tablets

Zentair

WARNINGS: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B, PATIENTS CO-INFECTED WITH HIV AND HBV, and LACTIC ACIDOSIS AND HEPATOMEGALY
Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted [see WARNINGS AND PRECAUTIONS].
Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if ZENTAIR is used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated.
Therapy with ZENTAIR is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) [see WARNINGS AND PRECAUTIONS].
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals [see WARNINGS AND PRECAUTIONS].

COMPOSITION
ZENTAIR 0.5 mg
Each film-coated tablet contains:
Entecavir ..... 0.5 mg
Colour: Titanium Dioxide

ZENTAIR 1.0 mg
Each film-coated tablet contains:
Entecavir ..... 1.0 mg
Colours: Titanium Dioxide & Red Oxide of Iron

DOSAGE FORM
Oral, film-coated tablet

PHARMACOLOGY
Pharmacodynamics
Mechanism of Action
Entecavir is an antiviral drug. Entecavir, a guanosine nucleoside analogue with activity against HBV reverse transcriptase (rt), is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate, deoxyguanosine triphosphate, entecavir triphosphate functionally inhibits all three activities of the HBV reverse transcriptase: (1) Base priming, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand of HBV DNA. Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases α, β, and δ and mitochondrial DNA polymerase gamma with K_i values ranging from 18 to >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 lamivudine-resistant HBV (rtL180M, rtM204V) was 0.026 μM (range: 0.010 to 0.059 μM).The co-administration of HIV nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) with entecavir is unlikely to reduce the antiviral efficacy of entecavir against HBV or of any of these agents against HIV. 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 was not antagonistic to the cell culture anti-HIV activity of these six NRTIs or emtricitabine at concentrations greater than 100 times the C_{max} of entecavir using the 1 mg dose.

Antiviral Activity against HIV
Analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical HIV type 1 (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 in HIV reverse transcriptase at micromolar concentrations, confirming inhibitory pressure at high entecavir concentrations. HIV variants containing the M184V substitution showed loss of susceptibility to entecavir.

Pharmacokinetics
The single- and multiple-dose pharmacokinetics of entecavir were evaluated in healthy subjects and subjects with chronic HBV infection.

Absorption
Following oral administration in healthy subjects, entecavir peak plasma concentrations occurred between 0.5 and 1.5 hours. Following multiple daily doses ranging from 0.1 to 1.0 mg, C_{max} and area under the concentration-time curve (AUC) at steady state increased in proportion to dose. Steady state was achieved after 6 to 10 days of once-daily administration with approximately 2-fold accumulation. For a 0.5 mg oral dose, C_{max} at steady state was 4.2 ng/mL and trough plasma concentration (C_{trough}) was 0.3 ng/mL. For a 1 mg oral dose, C_{max} was 8.2 ng/mL and C_{trough} was 0.5 ng/mL.
Effects of Food on Oral Absorption: Oral administration of 0.5 mg of entecavir 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 delay in absorption (1.0–1.5 hours fed versus 0.75 hours fasted), a decrease in C_{max} of 44–46%, and a decrease in AUC of 18–20% [see **DOSAGE AND ADMINISTRATION**].

Distribution
Based on the pharmacokinetic profile of entecavir after oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that entecavir is extensively distributed into tissues. Binding of entecavir to human serum proteins *in vitro* was approximately 13%.

Metabolism and Elimination
Following administration of ^{14}C-entecavir in humans and rats, no oxidative or acetylated metabolites were observed. Minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system [see **Drug Interactions**].
After reaching peak concentration, 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 approximately 24 hours.
Entecavir is predominantly eliminated by the kidneys, with urinary recovery of the unchanged drug at steady state ranging from 62% to 73% of the administered dose. Renal clearance is independent of dose and ranges from 360 to 471 mL/min, suggesting that entecavir undergoes both glomerular filtration and net tubular secretion [see **Drug Interactions**].

Special Populations
Gender: There are no significant gender differences in entecavir pharmacokinetics.
Race: There are no significant racial differences in entecavir pharmacokinetics.
Elderly: The effect of age on the pharmacokinetics of entecavir was evaluated following administration of a single 1 mg oral dose in healthy young and elderly volunteers. Entecavir AUC was 29.3% greater in elderly subjects compared to young subjects. The disparity in exposure between elderly and young subjects was most likely attributable to differences in renal function. Dosage adjustment of **ZENTAIR Tablets** should be based on the renal function of the patient, rather than age [see **DOSAGE AND ADMINISTRATION**].
Pediatrics: Pharmacokinetic studies have not been conducted in children.
Renal Impairment: The pharmacokinetics of entecavir following a single 1 mg dose were studied in subjects (without chronic HBV infection) with selected degrees of renal impairment, including subjects whose renal impairment was managed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Results are shown in Table 1 [see **DOSAGE AND ADMINISTRATION**].

Table 1: Pharmacokinetic Parameters in Subjects with Selected Degrees of Renal Function

	Renal Function Group					
	Baseline Creatinine Clearance (mL/min)					
	Unimpaired >80 n=6	**Mild >50 to ≤80 n=6**	**Moderate 30 to 50 n=6**	**Severe <30 n=6**	**Severe managed with hemodialysis[a] n=6**	**Severe Managed with CAPD n=4**
C_{max} (ng/mL) (CV %)	8.1 (30.7)	10.4 (37.2)	10.5 (22.7)	15.3 (33.8)	15.4 (56.4)	16.6 (29.7)
$AUC_{(0-T)}$ (ng•h/mL) (CV)	27.9 (25.6)	51.5 (22.8)	69.5 (22.7)	145.7 (31.5)	233.9 (28.4)	221.8 (11.6)
CLR (mL/min) (SD)	383.2 (101.8)	197.9 (78.1)	135.6 (31.6)	40.3 (10.1)	NA	NA
CLT/F (mL/min) (SD)	588.1 (153.7)	309.2 (62.6)	226.3 (60.1)	100.6 (29.1)	50.6 (16.5)	35.7 (19.6)

[a] *Dosed immediately following hemodialysis.*
CLR = Renal clearance; CLT/F = Apparent oral clearance.

Following a single 1 mg dose of entecavir administered 2 hours before the hemodialysis session, hemodialysis removed approximately 13% of the entecavir dose over 4 hours. CAPD removed approximately 0.3% of the dose over 7 days [see **DOSAGE AND ADMINISTRATION**].
Hepatic Impairment: The pharmacokinetics of entecavir following a single 1 mg dose was studied in subjects (without chronic HBV infection) with moderate or severe hepatic impairment (Child-Pugh Class B or C). The pharmacokinetics of entecavir was similar between hepatically impaired and healthy control subjects; therefore, no dosage adjustment of **ZENTAIR Tablets** is recommended for patients with hepatic impairment.
Post-Liver Transplant: The safety and efficacy of **ZENTAIR Tablets** in liver transplant recipients are unknown. However, in a small pilot study of entecavir use in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4), entecavir exposure was approximately 2-fold the exposure in healthy subjects with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these subjects. The potential for pharmacokinetic interactions between entecavir and cyclosporine A or tacrolimus was not formally evaluated.

INDICATIONS
ZENTAIR **Tablets** (entecavir) are 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 entecavir:
•This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naïve and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative chronic HBV infection and 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 [see **UNDESIRABLE EFFECTS**].
•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 [see **WARNINGS AND PRECAUTIONS**].

DOSAGE AND ADMINISTRATION
ZENTAIR Tablets should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

Recommended Dosage
Compensated Liver Disease
The recommended dose of entecavir for chronic hepatitis B virus infection in nucleoside treatment-naïve adults and adolescents 16 years of age and older is 0.5 mg once daily.
The recommended dose of entecavir in adults and adolescents (at least 16 years of age) with a history of hepatitis B viremia while receiving lamivudine or known lamivudine or telbivudine resistance mutations rtM204I/V with or without rtL180M, rtL80I/V, or rtV173L is 1 mg once daily.

Decompensated Liver Disease
The recommended dose of entecavir for chronic hepatitis B virus infection in adults with decompensated liver disease is 1 mg once daily.

Duration of Therapy
The optimal duration of treatment with entecavir for patients with chronic hepatitis B virus infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

Renal Impairment
In subjects with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased. Dosage adjustment is recommended for patients with creatinine clearance less than 50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 2. The once-daily dosing regimens are preferred.

Table 2: Recommended Dosage of ZENTAIR Tablets in Patients with Renal Impairment

Creatinine Clearance (mL/min)	**Usual Dose (0.5 mg)**	**Lamivudine-Refractory or Decompensated**
≥50	0.5 mg once daily	**Liver Disease (1 mg)** 1 mg once daily
30 to <50	0.5 mg every 48 hours	0. 5 mg once daily **OR** 1 mg every 48 hours
10 to <30	0.5 mg every 72 hours	1 mg every 72 hours
<10 Hemodialysis[a] or CAPD	0.5 mg every 7 days	1 mg every 7 days

[a] *If administered on a hemodialysis day, administer **ZENTAIR Tablets** after the hemodialysis session.*

Hepatic Impairment
No dosage adjustment is necessary for patients with hepatic impairment.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Severe Acute Exacerbations of Hepatitis B
Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Patients Co-infected with HIV and HBV
Entecavir has not been evaluated in HIV/HBV co-infected patients who were not simultaneously receiving effective HIV treatment. Limited clinical experience suggests there is a potential for the development of resistance to HIV nucleoside reverse transcriptase inhibitors if entecavir is used to treat chronic HBV infection in patients with HIV infection that is not being treated. Therefore, therapy with entecavir is not recommended for HIV/HBV co-infected patients who are not also receiving HAART. Before initiating entecavir therapy, HIV antibody testing should be offered to all patients. Entecavir has not been studied as a treatment for HIV infection and is not recommended for this use.

Lactic Acidosis and Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with entecavir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal Impairment
Dosage adjustment of entecavir is recommended for patients with creatinine clearance less than 50 mL/min, including patients on hemodialysis or CAPD [see **DOSAGE AND ADMINISTRATION**].

Liver transplant recipients
The safety and efficacy of entecavir in liver transplant recipients are unknown. If entecavir treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function must be carefully monitored both before and during treatment with entecavir [see **DOSAGE AND ADMINISTRATION**].

Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies of entecavir in pregnant women. When pregnant rats and rabbits received entecavir at 28 and 212 times the human exposure at the highest human dose, there were no signs of embryofetal toxicity. Because animal reproduction studies are not always predictive of human response, entecavir should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

Labor and Delivery
There are no studies in pregnant women and no data on the effect of entecavir on transmission of HBV from the mother to the infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.

Lactation
It is not known whether entecavir is excreted into human milk; however, entecavir is excreted into the milk of rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from entecavir, a decision should be made to discontinue nursing or to discontinue entecavir taking into consideration the importance of continued hepatitis B therapy to the mother and the known benefits of breastfeeding.

Pediatric Use
Safety and effectiveness of entecavir in pediatric patients below the age of 16 years have not been established.

Geriatric Use
Clinical studies of entecavir did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Entecavir is substantially excreted by the kidneys and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see **DOSAGE AND ADMINISTRATION**].

Use in Racial/Ethnic Groups
Clinical studies of entecavir did not include sufficient numbers of subjects from some racial/ethnic minorities (Black/African American, Hispanic) to determine whether they respond differently to treatment with the drug. There are no significant racial differences in entecavir pharmacokinetics.

Drug Interactions
Entecavir is not a substrate, inhibitor, or inducer of the CYP450 enzyme system. The pharmacokinetics of entecavir is unlikely to be affected by co-administration with agents that are either metabolized by, inhibit, or induce the CYP450 system. Likewise, the pharmacokinetics of known CYP substrates are unlikely to be affected by co-administration of entecavir.
Since entecavir is primarily eliminated by the kidneys, co-administration of entecavir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the co-administered drug. Co-administration of entecavir with lamivudine, adefovir dipivoxil or tenofovir disoproxil fumarate did not result in significant drug interactions. The effects of co-administration of ZENTAIR **Tablets** with other drugs that are renally eliminated or are known to affect renal function have not been evaluated, and patients should be monitored closely for adverse events when ZENTAIR **Tablets** is co-administered with such drugs.

UNDESIRABLE EFFECTS
The following adverse reactions are discussed in other sections of the labeling:
- Exacerbations of hepatitis after discontinuation of treatment [see **BOXED WARNINGS; WARNINGS AND PRECAUTIONS**].
- Lactic acidosis and severe hepatomegaly with steatosis [see **BOXED WARNINGS; WARNINGS AND PRECAUTIONS**].

Adverse Reactions from Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Compensated Liver Disease
Assessment of adverse reactions is based on four studies (AI463014, AI463022, AI463026 and AI463027) in which 1720 subjects with chronic HBV infection received double-blind treatment with entecavir 0.5 mg/day (n=679), entecavir 1 mg/day (n=183), or lamivudine (n=858) for up to 2 years. Median duration of therapy was 69 weeks for entecavir-treated subjects and 63 weeks for lamivudine-treated subjects in Studies AI463022 and AI463027, and 73 weeks for entecavir-treated subjects and 51 weeks for lamivudine-treated subjects in Studies AI463026 and AI463014.
The most common adverse reactions of any severity (≥3%) with at least a possible relation to the study drug for entecavir-treated subjects were headache, fatigue, dizziness, and nausea. The most common adverse reactions among lamivudine-treated subjects were headache, fatigue, and dizziness. In these four studies, 1% of entecavir-treated subjects discontinued because of adverse events or abnormal laboratory test results, compared with 4% of lamivudine-treated subjects.
Clinical adverse reactions of moderate–severe intensity and considered at least possibly related to the treatment occurring during therapy in four clinical studies in which entecavir was compared with lamivudine are presented in Table 3.

Table 3: Clinical Adverse Reactions[a] of Moderate–Severe Intensity (Grades 2–4) Reported in Four Entecavir Clinical Trials over 2 Years

	Nucleoside-Naïve[b]		**Lamivudine-Refractory[c]**	
Body System/ Adverse Reaction	**Entecavir 0.5 mg n=679**	**Lamivudine 100 mg n=668**	**Entecavir 1 mg n=183**	**Lamivudine 100 mg n=190**
Any Grade 2–4 adverse reaction[a]	15%	18%	22%	23%
Gastrointestinal				
Diarrhea	<1%	0	1%	0
Dyspepsia	<1%	<1%	1%	0
Nausea	<1%	<1%	<1%	2%
Vomiting	<1%	<1%	<1%	0
General				
Fatigue	1%	1%	3%	3%
Nervous System				
Headache	2%	2%	4%	1%
Dizziness	<1%	<1%	0	1%
Somnolence	<1%	<1%	0	0
Psychiatric				
Insomnia	<1%	<1%	0	<1%

[a] *Includes events of possible, probable, certain, or unknown relationship to the treatment regimen.*

[b] *Studies AI463022 and AI463027.*

[c] *Includes Study AI463026 and the entecavir 1 mg and lamivudine treatment arms of Study AI463014, a Phase 2 multinational, randomized, double-blind study of three doses of entecavir (0.1, 0.5, and 1 mg) once daily versus continued lamivudine 100 mg once daily for up to 52 weeks in subjects who experienced recurrent viremia on lamivudine therapy.*

Laboratory Abnormalities
Frequencies of selected treatment-emergent laboratory abnormalities reported during therapy in four clinical trials of entecavir compared with lamivudine are listed in Table 4.

Table 4: Selected Treatment-Emergent[a] Laboratory Abnormalities Reported in Four Entecavir Clinical Trials over 2 Years

	Nucleoside-Naïve[b]		**Lamivudine-Refractory[c]**	
Test	**Entecavir 0.5 mg n=679**	**Lamivudine 100 mg n=668**	**Entecavir 1 mg n=183**	**Lamivudine 100 mg n=190**
Any Grade 3–4 laboratory abnormality[d]	35%	36%	37%	45%
ALT >10 × ULN and >2 × baseline	2%	4%	2%	11%
ALT >5.0 × ULN	11%	16%	12%	24%
Albumin <2.5 g/dL	<1%	<1%	0	2%
Total bilirubin > 2.5 × ULN	2%	2%	3%	2%
Lipase ≥2.1 × ULN	7%	6%	7%	7%
Creatinine >3.0 × ULN	0	0	0	0
Confirmed creatinine increase ≥0.5 mg/dL	1%	1%	2%	1%
Hyperglycemia, fasting >250 mg/dL	2%	1%	3%	1%
Glycosuria[e]	4%	3%	4%	6%
Hematuria[f]	9%	10%	9%	6%
Platelets <50,000/mm^3	<1%	<1%	<1%	<1%

[a] *On-treatment value worsened from baseline to Grade 3 or Grade 4 for all parameters except albumin (any on-treatment value <2.5 g/dL), confirmed creatinine increase ≥0.5 mg/dL, and ALT >10 × ULN and >2 × baseline.*

[b] *Studies AI463022 and AI463027.*

[c] *Includes Study AI463026 and the entecavir 1 mg and lamivudine treatment arms of Study AI463014, a Phase 2 multinational, randomized, double-blind study of three doses of entecavir (0.1, 0.5, and 1 mg) once daily versus continued lamivudine 100 mg once daily for up to 52 weeks in subjects who experienced recurrent viremia on lamivudine therapy.*

[d] *Includes hematology, routine chemistries, renal and liver function tests, pancreatic enzymes and urinalysis.*

[e] *Grade 3 = 3+, large, ≥500 mg/dL; Grade 4 = 4+, marked, severe.*

[f] *Grade 3 = 3+, large; Grade 4 = ≥4+, marked, severe, many.*

ULN = Upper limit of normal

Among the entecavir-treated subjects in these studies, on-treatment ALT elevations greater than ten times the ULN and greater than two times baseline generally resolved with continued treatment. A majority of these exacerbations were associated with a ≥2 $\log_{10}$/mL reduction in the viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of Hepatitis after Discontinuation of Treatment **[see WARNINGS AND PRECAUTIONS]**
An exacerbation of hepatitis or ALT flare was defined as ALT greater than ten times the ULN and greater than two times the subject's reference level (minimum of the baseline or last measurement at the end of dosing). For all subjects who discontinued treatment (regardless of reason), Table 5 presents the proportion of subjects in each study who experienced post-treatment ALT flares. In these studies, a subset of subjects was allowed to discontinue treatment at or after 52 weeks if they achieved a protocol-defined response to therapy. If entecavir is discontinued without regard to treatment response, the rate of post-treatment flares could be higher.

Table 5: Exacerbations of Hepatitis during Off-Treatment Follow-up with Subjects in Studies AI463022, AI463027, and AI463026

Subjects with ALT Elevations >10 ×ULN and >2 × Reference[a]		
	Entecavir	**Lamivudine**
Nucleoside-naïve		
HBeAg-positive	4/174 (2%)	13/147 (9%)
HBeAg-negative	24/302 (8%)	30/270 (11%)
Lamivudine-refractory	6/52 (12%)	0/16

[a] *Reference is the minimum of the baseline or last measurement at the end of dosing. Median time to off-treatment exacerbation was 23 weeks for entecavir-treated subjects and 10 weeks for lamivudine-treated subjects.*

Decompensated Liver Disease
Study AI463048 was a randomized, open-label study of entecavir 1 mg once daily versus adefovir dipivoxil 10 mg once daily given for up to 48 weeks in adult subjects with chronic HBV infection and evidence of hepatic decompensation, defined as a Child-Turcotte-Pugh (CTP) score of 7 or higher. Among the 102 subjects receiving entecavir, the most common treatment-emergent adverse events of any severity, regardless of causality, occurring through Week 48 were peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%). Clinical adverse reactions not listed in Table 3 that were observed through Week 48 include blood bicarbonate decreased (2%) and renal failure (<1%).
Eighteen of 102 (18%) subjects treated with entecavir and 18/89 (20%) subjects treated with adefovir dipivoxil died during the first 48 weeks of therapy. The majority of deaths (11 in the entecavir group and 16 in the adefovir dipivoxil group) were due to liver-related causes such as hepatic failure, hepatic encephalopathy, hepatorenal syndrome, and upper gastrointestinal hemorrhage. The rate of hepatocellular carcinoma (HCC) through Week 48 was 6% (6/102) for subjects treated with entecavir and 8% (7/89) for subjects treated with adefovir dipivoxil. Five percent of subjects in either treatment arm discontinued therapy due to an adverse event through Week 48.
No subject in either treatment arm experienced an on-treatment hepatic flare (ALT > 2 X baseline and > 10 X ULN) through Week 48. Eleven of 102 (11%) subjects treated with entecavir and 11/89 (13%) subjects treated with adefovir dipivoxil had a confirmed increase in serum creatinine of 0.5 mg/dL through Week 48.

HIV/HBV Co-infected
The safety profile of entecavir 1 mg (n=51) in HIV/HBV co-infected subjects enrolled in Study AI463038 was similar to that of placebo (n=17) through 24 weeks of blinded treatment and similar to that seen in non-HIV infected subjects [see **WARNINGS AND PRECAUTIONS].**

Postmarketing Experience
The following adverse reactions have been reported during the postmarketing use of entecavir. Because these reactions were reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to entecavir exposure.

Immune System Disorders: *Anaphylactoid reaction.*

Skin and Subcutaneous Tissue Disorders: *Alopecia, rash.*

Hepatobiliary disorders: *Increased transaminases*

Metabolism and nutrition disorders: *Lactic acidosis*

OVERDOSAGE
There is limited experience of entecavir overdosage reported in patients. Healthy subjects who received single entecavir doses up to 40 mg or multiple doses up to 20 mg/day for up to 14 days had no increase in or unexpected adverse events. If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.
Following a single 1 mg dose of entecavir, a 4-hour hemodialysis session removed approximately 13% of the entecavir dose.

STORAGE AND HANDLING INSTRUCTIONS : Do not store above 30°C

PACKAGING INFORMATION
ZENTAIR 0.5 mg Blister of 10 Tablets
ZENTAIR 1.0 mg Blister of 10 Tablets

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Cipla

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List of Misspelt words

S.No.	Word	Count