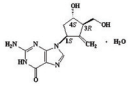
Virunix-B™ (Entecavir) Tablets

ویرونیکس ۔بی ٹیبلیٹس

QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains:
Entecavir as monohydrate U.S.P.....0.5mg

DESCRIPTION
Virunix-B (Entecavir) is the tradename for entecavir, a guanosine nucleoside analogue with selective activity against HBV. The chemical name for entecavir is 2-amino-1,9-dihydro-9-[(1S,3R,4S)-4 hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one, monohydrate. Its molecular formula is $C_{12}H_{15}N_5O_4 \bullet H_2O$, which corresponds to a molecular weight of 295.3.
Entecavir has the following structural formula:



WARNING: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B, PATIENTS CO-INFECTED WITH HIV AND HBV, AND LACTIC ACIDOSIS AND HEPATOMEGALY
Severe acute exacerbations of hepatitis B are known to occur 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.
There is a known potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if Entecavir is used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated. Therapy with Entecavir is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART).
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, are known to occur with the use of nucleoside analogue inhibitors alone or in combination with antiretroviral

CLINICAL INFORMATION
Indications
Virunix-B (Entecavir) is indicated for the treatment of chronic hepatitis B virus infection in adults and pediatric patients 2 years of age and older 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 Virunix-B (Entecavir):
- In adult patients, this indication is based on data in nucleoside-inhibitortreatment-naïve and lamivudine-resistant individuals with HBeAg-positive and HBeAg-negative HBV infection and compensated liver disease and a more limited number of individuals with decompensated liver disease.
- In pediatric patients 2 years of age and older, this indication is based on data in nucleoside-inhibitor-treatment-naïve and in a limited number of lamivudine-experienced individuals with HBeAg-positive chronic HBV infection and compensated liver disease.

Dosage and Administration
Adult dosage
Compensated liver disease
Nucleoside naive patients: the recommended dose in adults is 0.5 mg once daily, with or without food.
Lamivudine-refractory patients (i.e. with evidence of viraemia while on lamivudine or the presence of lamivudine resistance [LVDr] mutations): the recommended dose in adults is 1 mg once daily, which must be taken on an empty stomach (more than 2 hours before and more than 2 hours after a meal). In the presence of LVDr mutations, 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
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 (more than 2 hours before and more than 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 dosage
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.
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.
Dosage Adjustment
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). A reduction of the daily dose using Virunix-B (Entecavir) oral solution, as detailed in the table, is recommended. As an alternative, in case the oral solution is not available, the dose can be adjusted by increasing the dosage interval, also shown in the table. The proposed dose modifications are based on extrapolation of limited data, and their safety and effectiveness are not known. Therefore, virological response should be closely monitored.

	Virunix-B (Entecavir) dosage*	
Creatinine clearance (ml/min)	**Nucleoside naïve patients**	**Lamivudine-refractory or decompensated liver disease**
≥ 50	0.5 mg once daily	1 mg once daily
30 - 49	0.25 mg once daily* OR 0.5 mg every 48 hours	0.5 mg once daily
10 - 29	0.15 mg once daily* OR 0.5 mg every 72 hours	0.3 mg once daily* OR 0.5 mg every 48 hours
< 10 Haemodialysis or CAPD**	0.05 mg once daily* OR 0.5 mg every 5-7 days	0.1 mg once daily* OR 0.5 mg every 72 hours

* for doses < 0.5 mg Virunix-B (Entecavir) oral solution is recommended.
** on haemodialysis days, administer entecavir after haemodialysis.
Hepatic impairment: No dose adjustment is required in patients with hepatic impairment.
Geriatric Use
Entecavir is substantially excreted by the kidney, 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
Administration Requirements
Virunix-B (Entecavir) should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal). Virunix-B (Entecavir) should be taken orally.

Contraindications
Unknown

Warnings and Precautions
Exacerbations of hepatitis
Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterized 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 is also known to occur 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, are known to occur.
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) is known to occur 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 hypoxemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, are known to occur 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, are known to be 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 are present at baseline. Patients with lamivudine-resistant HBV are at higher risk of developing subsequent entecavir resistance than patients without lamivudine resistance. Virological response should be frequently monitored in the lamivudine-refractory patients 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
A lower rate of virologic response (HBV DNA < 50 IU/ml) is known in paediatric patients with baseline HBV DNA ≥ 8.0 $\log_{10}$ IU/ml. 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.
Human immunodeficiency virus (HIV) / HBV co-infected patients not receiving concomitant antiretroviral therapy
Entecavir is not known in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment. Emergence of HIV resistance is known to occur when entecavir 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 is not known 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 is insufficient 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 is not known to reduce the risk of transmission of HBV and therefore appropriate precautions should still be taken.

Interactions
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 are not known. Patients should be monitored closely for adverse reactions when entecavir is co administered with such medicinal products.
No pharmacokinetic interactions between entecavir and lamivudine, adefovir or tenofovir are known. 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. Interaction are only known in adults.

Pregnancy and Breastfeeding
Pregnancy Category: C
There is insufficient data of Entecavir in pregnant women. Entecavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
It is not known whether Entecavir is excreted into human milk. 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.

Effects on Ability to Drive and Use Machines
Effects on the ability to drive and use machines are not known. Dizziness, fatigue and somnolence are common side effects which may impair the ability to drive and use machines.

Adverse Reactions
In patients with compensated liver disease, the most common adverse reactions of any severity with at least a possible relation to entecavir are headache, fatigue, dizziness and nausea. Exacerbations of hepatitis during and after discontinuation of entecavir therapy are also known to occur.
Adverse reactions considered at least possibly related to treatment with entecavir are listed by body system organ class.

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 are known to occur, often in association with hepatic decompensation, other serious medical conditions or drug exposures.
Treatment beyond 48 weeks: continued treatment with entecavir for a median duration of 96 weeks is not known to reveal any new safety signals.

Overdose
There is insufficient data available of entecavir overdose. Healthy individuals who receive up to 20 mg/day for up to 14 days, and single doses up to 40 mg are known to have no unexpected adverse reactions. If overdose occurs, the patient must be monitored for evidence of toxicity and given standard supportive treatment as necessary.

PHARMACOLOGICAL PROPERTIES
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 has no relevant adverse effects on γ polymerase or mitochondrial DNA synthesis in HepG2 cells (K_i > 160 µM).
Pharmacokinetic Properties
Absorption
Entecavir is rapidly absorbed with peak plasma concentrations occurring between 0.5-1.5 hours. The absolute bioavailability is not known. Based on urinary excretion of unchanged drug, the bioavailability to be 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 ≈ 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.
Administration of 0.5 mg entecavir with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) results in a minimal delay in absorption (1-1.5 hour fed vs. 0.75 hour fasted), a decrease in C_{max} of 44-46%, and a decrease in AUC of 18-20%. The lower C_{max} 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%.
Metabolism
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, are known.
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 known drug accumulation index is ≈ 2 times with once daily dosing, suggesting an effective accumulation half-life of about 24 hours.

PHARMACEUTICAL INFORMATION
Shelf Life
2 years.

Special Precautions for Storage
- Do not store above 30 °C.
- Keep all medicines out of reach of children.
- Protect from light and moisture.

Nature and Contents of Container
VIRUNIX-B (Entecavir) 0.5 mg tablets are supplied in a blister of 30s (3 x 10's).

Manufactured by:

ASPIN
An OBS Group Company

Aspin Pharma (Pvt.) Ltd.
Plot No. 10 & 25, Sector No. 20, Korangi Industrial Area,
Karachi - 74900, Pakistan.
www.aspin.com.pk

REVISION DATE
February 2020

ہدایات :
صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔
۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

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دوا کو روشنی اور نمی سے بچا کر رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔

VB-L-4/1