ly active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain termination.
Tenofovir has activity that is specific to hepatitis B virus and human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in vitro based on several assays including mitochondrial DNA analyses.

Pharmacokinetic properties:
Absorption:
Following oral administration of tenofovir alafenamide under fasted conditions in adult patients with chronic hepatitis B, peak plasma concentrations of tenofovir alafenamide were observed approximately 0.48 hours post-dose. Relative to fasting conditions, the administration of a single dose of tenofovir alafenamide with a high fat meal resulted in a 65% increase in tenofovir alafenamide exposure.

Distribution:
The binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%. The binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01-25 µg/mL.

Biotransformation:
Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. In vivo, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate.

Elimination:
Tenofovir is renally eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

Pharmacokinetics in special populations:
Age, gender and ethnicity
No clinically relevant differences in pharmacokinetics according to age or ethnicity have been identified. Differences in pharmacokinetics according to gender were not considered to be clinically relevant.
Hepatic impairment
In patients with severe hepatic impairment, total plasma concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in severe hepatic impairment and normal hepatic function are similar.

SPECIAL PRECAUTIONS FOR STORAGE
Store in the original package in order to protect from moisture.

STORAGE CONDITIONS AND OTHER INFORMATION
• Store below 30°C in a dry place, protect from light.
• To be dispensed on the prescription of a registered Medical practitioner only.
• Keep out of the reach of children.

PRESENTATION:
Virteno 25mg tablet is available in blister packs 10's, 20's, 30's.

- خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

- دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
- صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔
- بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.,
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Art no: 619

Virteno®

(Tenofovir Alafenamide)

25mg Tablet

ورٹینو ۲۵ ملی گرام گولیاں
(ٹینوفوِر ایلافینا مائیڈ)

Virteno 25mg Tablets
Each film coated tablet contains:
Tenofovir Alafenamide (As Fumarate) ..... 25 mg.

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT SEVERE ACUTE EXACERBATION OF HEPATITIS B
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs. Discontinuation of anti-hepatitis B therapy, including Virteno, may result in severe acute exacerbations of hepatitis B. 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, including Virteno. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

CLINICAL PARTICULARS
Therapeutic indications
Virteno is indicated for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 kg).

Posology and method of administration
Therapy should be initiated by a physician experienced in the management of chronic hepatitis B.

Posology
Adults and adolescents (aged 12 years and older with body weight at least 35 kg): one tablet once daily.

Treatment discontinuation
Treatment discontinuation may be considered as follows:
• In HBeAg-positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or until there is loss of efficacy. Regular reassessment is recommended after treatment discontinuation to detect virological relapse.

• In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or until 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.

Missed dose
If a dose is missed and less than 18 hours have passed from the time it is usually taken, the patient should take Virteno as soon as possible and then resume their normal dosing schedule. If more than 18 hours have passed from the time it is usually taken, the patient should not take the missed dose and should simply resume the normal dosing schedule. If the patient vomits within 1 hour of taking Virteno, the patient should take another tablet. If the patient vomits more than 1 hour after taking Virteno, the patient does not need to take another tablet.

Special populations
Elderly
No dose adjustment of Virteno is required in patients aged 65 years and older
Renal impairment
No dose adjustment of Virteno is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥ 15 mL/min or in patients with CrCl < 15 mL/min who are receiving haemodialysis.
Hepatic impairment
No dose adjustment of Virteno is required in patients with hepatic impairment.
Paediatric population
The safety and efficacy of Virteno in children younger than 12 years of age, or weighing < 35 kg, have not yet been established. No data are available.

Method of administration
Oral administration. Virteno film-coated tablets should be taken with food.

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

WARNINGS AND PRECAUTIONS

Lactic Acidosis/Severe

Hepatomegaly with Steatosis Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate in combination with other 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 Virteno 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).

Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment

Discontinuation of anti-hepatitis B therapy, including Virteno, may result in severe acute exacerbations of hepatitis B. Patients who discontinue Virteno should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

HBV transmission

Patients must be advised that Virteno does not prevent the risk of transmission of HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Patients with decompensated liver disease

There are limited data on the safety and efficacy of Protenovir in HBV infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9 (i.e. class C). These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Renal impairment

Patients with creatinine clearance < 30 mL/min

There are very limited data on the safety and efficacy of Virteno in HBV-infected patients with CrCl < 15 mL/min on chronic haemodialysis.
The use of Virteno is not recommended in patients with CrCl < 15 mL/min who are not receiving haemodialysis.

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded.
It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with Virteno and that it is also monitored during therapy in all patients as clinically appropriate.

Co-administration with other medicinal products

Virteno should not be co-administered with medicinal products containing tenofovir alafenamide, tenofovir disoproxil or adefovir dipivoxil.
Co-administration of Protenovir with certain anticonvulsants (e.g. carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g. rifampicin, rifabutin and rifapentine) or St. John's wort, all of which are inducers of P-glycoprotein (P-gp) and may decrease tenofovir alafenamide plasma concentrations, is not recommended.
Co-administration of Virteno with strong inhibitors of P-gp (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Co-administration is not recommended.

Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.
Virteno should not be co-administered with medicinal products containing tenofovir disoproxil, tenofovir alafenamide or adefovir dipivoxil.

Medicinal products that may affect tenofovir alafenamide

Tenofovir alafenamide is transported by P-gp and breast cancer resistance protein (BCRP). Medicinal products that are P-gp inducers (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital or St. John's wort) are expected to decrease plasma concentrations of tenofovir alafenamide, which may lead to loss of therapeutic effect of Virteno.
Co-administration of such medicinal products with Virteno is not recommended.
Co-administration of tenofovir alafenamide with medicinal products that inhibit P-gp and BCRP may increase plasma concentrations of tenofovir alafenamide. Co-administration of strong inhibitors of P-gp with tenofovir alafenamide is not recommended.

Effect of tenofovir alafenamide on other medicinal products

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 in vitro. It is not an inhibitor or inducer of CYP3A in vivo.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women. However, a large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor feto/neonatal toxicity associated with the use of tenofovir disoproxil.
The use of tenofovir alafenamide may be considered during pregnancy, if necessary.

Breast-feeding

It is not known whether tenofovir alafenamide is secreted in human milk. However, in animal studies it has been shown that tenofovir is secreted into milk. There is insufficient information on the effects of tenofovir in newborns/infants.
A risk to the breast-fed newborns/infants cannot be excluded; therefore, tenofovir alafenamide should not be used during breast-feeding.

Fertility

No human data on the effect of tenofovir alafenamide on fertility are available. Animal studies do not indicate harmful effects of tenofovir alafenamide on fertility.

Effects on ability to drive and use machines

Virteno has no or negligible influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with tenofovir alafenamide.

UNDESIRABLE EFFECTS

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with tenofovir alafenamide in patients with chronic hepatitis B. The adverse reactions are listed below by body system organ class and frequency based on the Week 96 analysis. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to < 1/100).

Adverse drug reactions identified with tenofovir alafenamide

SYSTEM ORGAN CLASS	
Frequency	**Adverse reaction**
Nervous system disorders	
Very common	Headache
Common	Dizziness
Gastrointestinal disorders	
Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence.
Hepatobiliary disorders	
Common	Increased ALT
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Angioedema, urticaria
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
General disorders and administration site conditions	
Common	Fatigue

Overdose

If overdose occurs the patient must be monitored for evidence of toxicity.
Treatment of overdose with tenofovir alafenamide consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether tenofovir can be removed by peritoneal dialysis.

CLINICAL PHARMACOLOGY:

Pharmacodynamic properties:

Pharmacotherapeutic group: Antiviral for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors.

Mechanism of action

Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is primarily hydrolysed to form tenofovir by carboxylesterase 1 in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated to the pharmacological-