Wymly® 25mg

(Tenofovir Alafenamide)
Tablets

وِملی ۲۵ ملی گرام

(تینوفوِرِ ایلافینامائیڈ)
ٹیبلٹس

QUALITATIVE AND QUANTITATIVE COMPOSITION

Wymly® Tablet 25mg

Each film- coated tablet contains: Tenofovir Alafenamide Fumarate eq. to
Tenofovir Alafenamide……25mg
Innovator's Specification

BOXED WARNING

Post Treatment Severe Acute Exacerbation Of Hepatitis B: Discontinuation of anti-hepatitis B therapy may result in severe acute exacerbations of hepatitis B. Hepatic function should be monitored closely in patients who discontinue Wymly. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

DESCRIPTION

Wymly is a tablet containing Tenofovir Alafenamide for oral administration. Tenofovir Alafenamide, a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

CLINICAL PHARMACOLOGY

Mechanism of Action: Tenofovir Alafenamide is an antiviral drug against the hepatitis B virus. Tenofovir Alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Tenofovir Alafenamide as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir Alafenamide is then converted to Tenofovir through hydrolysis primarily by carboxylesterase 1 (CES1) in primary hepatocytes. Intracellular Tenofovir is subsequently phosphorylated by cellular kinases to the pharmacologically active metabolite Tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chaintermination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Pharmacodynamics: Cardiac Electrophysiology, In a thorough QT/QTc study in 48 healthy subjects, Tenofovir Alafenamide at the recommended dose or at a dose 5 times the recommended dose did not affect the QT/QTc interval and did not prolong the PR interval.

Pharmacokinetics: Pharmacokinetic Properties of Wymly

Absorption	**Tenofovir Alafenamide**
Tmax (h)	0.48
Effect of high fat meal (relative to fasting): AUC_{last} Ratio[a]	1.65 (1.51, 1.81)
Distribution	
% Bound to human plasma proteins	80%
Source of protein binding data	Ex vivo
Blood-to-plasma ratio	1.0
Metabolism	
Metabolism[b]	CES1 (hepatocytes) Cathepsin A (PBMCs) CYP3A (minimal)
Elimination	
Major route of elimination	Metabolism (>80% of oral dose)
$t_{1/2}$ (h)[C]	0.51
% of dose excreted in urine[d]	<1
% of dose excreted in feces[d]	31.7

CES1 = carboxylesterase 1; PBMCs = peripheral blood mononuclear cells. a. Values refer to geometric mean ratio in AUC last [fed/fasted] and (90% confidence interval). High fat meal = ~800 kcal, 50% fat. b. In vivo, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In vitro studies have shown that TAF is metabolized to tenofovir by CES1 in hepatocytes, and by cathepsin A in PBMCs and macrophages. c. t1/2 values refer to median terminal plasma half-life. d. Dosing in mass balance study: TAF 25 mg (single dose administration of [14C] TAF).

INDICATIONS AND USAGE

It is indicated for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease.

CONTRAINDICATIONS

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

INTERACTIONS

Potential for Other Drugs to Affect Wymly: Tenofovir Alafenamide is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P- gp and BCRP activity may lead to changes in Tenofovir Alafenamide absorption. Drugs that induce P-gp activity are expected to decrease the absorption of Tenofovir Alafenamide, resulting in decreased plasma concentrations of Tenofovir Alafenamide, which may lead to loss of therapeutic effect of Wymly. Co-administration of Wymly with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of Tenofovir Alafenamide.

Drugs Affecting Renal Function: Because Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, co-administration of Wymly with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of Tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gen-tamicin), and high-dose or multiple NSAIDs.

Established and Other Potentially Significant Interactions:

Concomitant Drug Class: Drug name	Effect on concentration[b]	Clinical comment
Anticonvulsants: carbamazepine[c]* oxcarbazepine* phenobarbital* phenytoin*	↓Tenofovir Alafenamide	When co-administered with carbamazepine, the Tenofovir Alafenamide dose should be increased to two tablets once daily. Co-administration with oxcarbazepine, phenobarbital, or phenytoin is not recommended.
Antimycobacterial: Rifabutin* Rifampin* Rifapentine*	↓Tenofovir Alafenamide	Co-administration of Wymly with rifabutin, rifampin or rifapentine is not recommended.
Herbal Products: St. John's wort* (Hypericum perforatum)	↓Tenofovir Alafenamide	Co-administration of Wymly with St. John's wort is not recommended.

a. This table is not all inclusive.
b.= decrease.
c. Indicates that a drug interaction study was conducted.
* P-gp inducer

Drugs without Clinically Significant Interactions with Wymly:

Based on drug interaction studies conducted with Tenofovir Alafenamide, no clinically significant drug interactions have been observed with: ethinyl estradiol, itraconazole, ketoconazole, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, and sofosbuvir.

USE IN SPECIAL POPULATION

Pregnancy: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Wymly during pregnancy. There is no human data on the use of Wymly in

pregnant women to inform a drug-associated risks of adverse fetal developmental outcome.
Breast feeding: It is not known whether Wymly and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. A risk to the breastfed child cannot be excluded; therefore, Wymly should not be used during breast-feeding.
Renal impairment: No dosage adjustment of Wymly is required in patients with mild, moderate, or severe renal impairment. Wymly is not recommended in patients with end stage renal disease (estimated creatinine clearance below 15 ml per minute).
Hepatic Impairment: No dosage adjustment of Wymly is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Wymly in patients with decompensated. Cirrhosis (Child-Pugh B or C) have not been established; therefore Wymly is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment.
Pediatric Use: Safety and effectiveness of Wymly in pediatric patients less than 18 years of age have not been established.
Geriatric Use: No dose adjustment of Wymly is required in patients aged 65 years and older.

PRECAUTIONS

Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment: Discontinuation of anti-hepatitis B therapy, including Wymly, may result in severe acute exacerbations of hepatitis B.
Patients who discontinue Wymly 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 warrant-ed.
Risk of Development of HIV-1 Resistance in Patients Coinfected with HBV and HIV-1: Due to the risk of development of HIV-1 resistance, Wymly alone is not recommended for the treatment of HIV-1 infection. The safety and efficacy of Tenofovir Alafenamide have not been established in patients coinfected with HBV and HIV-1. HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with Tenofovir Alafenamide, and, if positive, an appropriate antiretroviral combination regimen that is recommended for patients co-infected with HIV-1 should be used.
New Onset or Worsening Renal Impairment: Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of Tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of Wymly, there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). Patients taking Tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents, including non-steroidal anti-inflammatory drugs, are at increased risk of developing renalrelated adverse reactions. It is recommended that serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating Wymly and during therapy in all patients as clinically appropriate. Discontinue Wymly in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.
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 DF, another prodrug of Tenofovir, alone or in combination with other antiretrovirals. Treatment with Wymly 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).

ADVERSE REACTIONS

- Severe Acute Exacerbation of Hepatitis B.
- New Onset or Worsening of Renal Impairment.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis.

DOSAGE AND ADMINISTRATION

Wymly 25 mg (one tablet) taken orally once daily with food. Prior to initiation of Wymly, patients should be tested for HIV-1 infection. Wymly alone should not be used in patients with HIV infection as mentioned in precautions. It is recommended that serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating Wymly and during therapy in all patients as clinically appropriate.

Overdosage: If overdose occurs, monitor patient for evidence of toxicity. Treatment of overdosage with Wymly 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 hemodialysis with an extraction coefficient of approximately 54%.

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 Wymly 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 , the patient should take another tablet. If the patient vomits more than 1 hour after taking , the patient does not need to take another tablet.

DOSAGE:

As directed by the physician.

INSTRUCTIONS

Store below 30°C. Protect from sunlight and moisture.

Keep all medicines out of the reach of children.

PRESENTATION

Wymly Tablets 25mg are available in Alu-Alu blister pack of 3x10's tablets.

علامات/طریقہ استعمال: وِلی ٹیبلٹس ہیپاٹائیٹس بی اور جگر کے امراض میں مبتلا مریضوں کے علاج کے لئے تجویز کردہ ہے۔

وِلی ٹیبلٹس ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

مضر اثرات: گردوں کی خرابی، لیکٹک ایسیڈوسس، ہیپیٹومیگیلی اور اسٹیوسس۔

احتیاطی تدابیر: حاملہ خواتین احتیاط سے استعمال کریں۔

دودھ پلانے والی ماؤں میں وِلی کا استعمال ممنوع ہے۔

بچوں، ڈیکمپنسیٹڈ جگر کے امراض میں مبتلا مریضوں اور گردے کے مریضوں میں وِلی کا استعمال ممنوع ہے۔

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم پر رکھیں۔ سورج کی روشنی، گرمی اور نمی سے محفوظ رکھیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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