

MYTAF 25 mg
TENOFOVIR ALAFENAMIDE TABLETS

1. NAME OF THE MEDICINAL PRODUCT

MYTAF 25 mg (Tenofovir Alafenamide Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet contains:

Tenofovir Alafenamide fumarate equivalent to Tenofovir Alafenamide 25 mg.

Excipients with known effects

Each film-coated tablet contains 67.957 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet;

A white to off-white, film-coated, round, biconvex tablet debossed with **M** on one side of the tablet and **TFI** on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenofovir Alafenamide is indicated for the treatment of chronic hepatitis B (CHB) in adults and adolescents (aged 12 years and older with body weight at least 35 kg) (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of CHB.

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 (see section 4.4):

- 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 (see section 4.4). 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 this medicinal product 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 treatment, the patient should take another tablet. If the patient vomits more than 1 hour after taking the treatment, the patient does not need to take another tablet.

Special populations

Elderly

No dose adjustment of this medicinal product is required in patients aged 65 years and older (see section 5.2).

Renal impairment

No dose adjustment of this medicinal product 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 $\text{CrCl} < 15$ mL/min who are receiving haemodialysis.

On days of haemodialysis, this medicinal product should be administered after completion of haemodialysis treatment (see section 5.2).

No dosing recommendations can be given for patients with $\text{CrCl} < 15$ mL/min who are not receiving haemodialysis (see section 4.4).

No data are available to make dose recommendations in children aged less than 12 years and of less than 35 kg body weight with renal impairment.

Hepatic impairment

No dose adjustment of this medicinal product is required in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of this medicinal product in children younger than 12 years of age, and weighing < 35 kg, have not yet been established. No data are available.

Method of administration

Oral use. Tenofovir alafenamide film-coated tablets should be taken with food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatitis B Virus (HBV) transmission

Patients must be advised that this medicinal product 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 tenofovir alafenamide 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 (see section 5.2).

Exacerbation of hepatitis

Flares on treatment

Spontaneous exacerbations in CHB are relatively common and are characterised by transient increases in serum alanine aminotransferase (ALT). After initiating antiviral therapy, serum ALT may increase in some patients. 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 cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation

Acute exacerbation of hepatitis has been reported in patients who have discontinued treatment for CHB, usually in association with rising HBV DNA levels in plasma. The majority of cases are self-limited but severe exacerbations, including fatal outcomes, may occur after discontinuation of treatment for CHB. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of treatment for CHB. If appropriate, resumption of CHB therapy may be warranted.

In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Renal impairment

Patients with creatinine clearance < 30 mL/min

The use of tenofovir alafenamide once daily in patients with $\text{CrCl} \geq 15 \text{ mL/min}$ and $< 30 \text{ mL/min}$ is based on Week 96 data on the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in an open-label clinical study of virologically suppressed HBV-infected patients (see sections 4.8 and 5.1). There are very limited data on the safety and efficacy of tenofovir alafenamide in HBV-infected patients with $\text{CrCl} < 15 \text{ mL/min}$ on chronic haemodialysis (see sections 4.8, 5.1 and 5.2).

The use of this medicinal product is not recommended in patients with $\text{CrCl} < 15 \text{ mL/min}$ who are not receiving haemodialysis (see section 4.2).

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with this treatment and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function, or evidence of proximal renal tubulopathy, discontinuation of this medicinal product should be considered.

Patients co-infected with HBV and hepatitis C or D virus

There are no data on the safety and efficacy of tenofovir alafenamide in patients co-infected with hepatitis C (HCV) or D (HDV) virus. Co-administration guidance for the treatment of HCV should be followed (see section 4.5).

HBV and Human Immunodeficiency Virus (HIV) co-infection

HIV antibody testing should be offered to all HBV-infected patients whose HIV-1 infection status is unknown before initiating therapy with this medicinal product. In patients who are co-infected with HBV and HIV, Tenofovir alafenamide should be co-administered with other antiretroviral medicinal products to ensure that the patient receives an appropriate regimen for treatment of HIV (see section 4.5).

Co-administration with other medicinal products

This medicinal product should not be co-administered with medicinal products containing tenofovir alafenamide, tenofovir disoproxil or adefovir dipivoxil.

Co-administration of this treatment 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 this treatment with strong inhibitors of P-gp (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Co-administration is not recommended.

Excipients with known effect

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

This medicinal product 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 Tenofovir alafenamide. Co-administration of such medicinal products with tenofovir alafenamide 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.

Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and/or OATP1B3.

Effect of tenofovir alafenamide on other medicinal products

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

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes.

Drug interaction information for Tenofovir alafenamide with potential concomitant medicinal products is summarised in Table 1 below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”; twice daily as “b.i.d.”, single dose as “s.d.”, once daily as “q.d.”). The drug interactions described are based on studies conducted with tenofovir alafenamide, or are potential drug interactions that may occur with Tenofovir alafenamide.

Table 1: Interactions Between Tenofovir alafenamide and Other Medicinal Products

Medicinal product by therapeutic areas	Effects on drug levels.	Recommendation concerning co-administration with Tenofovir alafenamide
ANTICONVULSANTS		
Carbamazepine (300 mg orally, b.i.d.)	<i>Tenofovir alafenamide</i> ↓ C _{max} ↓ AUC	Co-administration is not recommended.
Tenofovir alafenamide ^a (25 mg orally, s.d.)	<i>Tenofovir</i> ↓ C _{max} ↔ AUC	

Medicinal product by therapeutic areas	Effects on drug levels.	Recommendation concerning co-administration with Tenofovir alafenamide
Oxcarbazepine Phenobarbital	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Phenytoin	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Midazolam ^b (2.5 mg orally, s.d.) Tenofovir alafenamide ^a (25 mg orally, q.d.)	<i>Midazolam</i> ↔ C _{max} ↔ AUC	No dose adjustment of midazolam (administered orally or intravenously) is required.
Midazolam ^b (1 mg IV, s.d.) Tenofovir alafenamide ^a (25 mg orally, q.d.)	<i>Midazolam</i> ↔ C _{max} ↔ AUC	
ANTIDEPRESSANTS		
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide ^c (10 mg orally, q.d.)	<i>Tenofovir alafenamide</i> ↔ C _{max} ↔ AUC <i>Tenofovir</i> ↔ C _{max} ↔ AUC ↔ C _{min}	No dose adjustment of Tenofovir alafenamide or sertraline is required.
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide ^c (10 mg orally, q.d.)	<i>Sertraline</i> ↔ C _{max} ↔ AUC	
ANTIFUNGALS		
Itraconazole Ketoconazole	Interaction not studied. <i>Expected:</i> ↑ Tenofovir alafenamide	Co-administration is not recommended.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Rifabutin	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
HCV ANTIVIRAL AGENTS		

Medicinal product by therapeutic areas	Effects on drug levels.	Recommendation concerning co-administration with Tenofovir alafenamide
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied. <i>Expected:</i> ↔ Sofosbuvir ↔ GS-331007	No dose adjustment of Tenofovir alafenamide or sofosbuvir is required.
Ledipasvir/sofosbuvir (90 mg/400 mg orally, q.d.) Tenofovir alafenamide ^d (25 mg orally, q.d.)	<i>Ledipasvir</i> ↔ C _{max} ↔ AUC ↔ C _{min} <i>Sofosbuvir</i> ↔ C _{max} ↔ AUC <i>GS-331007^e</i> ↔ C _{max} ↔ AUC ↔ C _{min} <i>Tenofovir alafenamide</i> ↔ C _{max} ↔ AUC <i>Tenofovir</i> ↑ C _{max} ↑ AUC ↑ C _{min}	No dose adjustment of Tenofovir alafenamide or ledipasvir/sofosbuvir is required.
Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)	Interaction not studied. <i>Expected:</i> ↔ Sofosbuvir ↔ GS-331007 ↔ Velpatasvir ↑ Tenofovir alafenamide	No dose adjustment of Tenofovir alafenamide or sofosbuvir/velpatasvir is required.
Sofosbuvir/velpatasvir/voxilaprevir (400 mg/100 mg/ 100 mg + 100 mg ^g orally, q.d.) Tenofovir alafenamide ^d (25 mg orally, q.d.)	<i>Sofosbuvir</i> ↔ C _{max} ↔ AUC <i>GS-331007^e</i> ↔ C _{max} ↔ AUC <i>Velpatasvir</i> ↔ C _{max} ↔ AUC ↔ C _{min} <i>Voxilaprevir</i> ↔ C _{max} ↔ AUC ↔ C _{min} <i>Tenofovir alafenamide</i> ↑ C _{max} ↑ AUC	No dose adjustment of Tenofovir alafenamide or sofosbuvir/velpatasvir/voxilaprevir is required.

Medicinal product by therapeutic areas	Effects on drug levels.	Recommendation concerning co-administration with Tenofovir alafenamide
HIV ANTIRETROVIRAL AGENTS – PROTEASE INHIBITORS		
Atazanavir/cobicistat (300 mg/150 mg orally, q.d.) Tenofovir alafenamide ^a (10 mg orally, q.d.)	<i>Tenofovir alafenamide</i> ↑ C _{max} ↑ AUC <i>Tenofovir</i> ↑ C _{max} ↑ AUC ↑ C _{min} <i>Atazanavir</i> ↔ C _{max} ↔ AUC ↔ C _{min} <i>Cobicistat</i> ↔ C _{max} ↔ AUC ↑ C _{min}	Co-administration is not recommended.
Atazanavir/ritonavir (300 mg/100 mg orally, q.d.) Tenofovir alafenamide ^a (10 mg orally, s.d.)	<i>Tenofovir alafenamide</i> ↑ C _{max} ↑ AUC <i>Tenofovir</i> ↑ C _{max} ↑ AUC <i>Atazanavir</i> ↔ C _{max} ↔ AUC ↔ C _{min}	Co-administration is not recommended.
Darunavir/cobicistat (800 mg/150 mg orally, q.d.) Tenofovir alafenamide ^a (25 mg orally, q.d.)	<i>Tenofovir alafenamide</i> ↔ C _{max} ↔ AUC <i>Tenofovir</i> ↑ C _{max} ↑ AUC ↑ C _{min} <i>Darunavir</i> ↔ C _{max} ↔ AUC ↔ C _{min} <i>Cobicistat</i> ↔ C _{max} ↔ AUC ↔ C _{min}	Co-administration is not recommended.

Medicinal product by therapeutic areas	Effects on drug levels.	Recommendation concerning co-administration with Tenofovir alafenamide
Darunavir/ritonavir (800 mg/100 mg orally, q.d.) Tenofovir alafenamide ^a (10 mg orally, s.d.)	<i>Tenofovir alafenamide</i> ↑ C _{max} ↔ AUC <i>Tenofovir</i> ↑ C _{max} ↑ AUC <i>Darunavir</i> ↔ C _{max} ↔ AUC ↔ C _{min}	Co-administration is not recommended.
Lopinavir/ritonavir (800 mg/200 mg orally, q.d.) Tenofovir alafenamide ^a (10 mg orally, s.d.)	<i>Tenofovir alafenamide</i> ↑ C _{max} ↑ AUC <i>Tenofovir</i> ↑ C _{max} ↑ AUC <i>Lopinavir</i> ↔ C _{max} ↔ AUC ↔ C _{min}	Co-administration is not recommended.
Tipranavir/ritonavir	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
HIV ANTIRETROVIRAL AGENTS – INTEGRASE INHIBITORS		
Dolutegravir (50 mg orally, q.d.) Tenofovir alafenamide ^a (10 mg orally, s.d.)	<i>Tenofovir alafenamide</i> ↑ C _{max} ↑ AUC <i>Tenofovir</i> ↔ C _{max} ↑ AUC <i>Dolutegravir</i> ↔ C _{max} ↔ AUC ↔ C _{min}	No dose adjustment of Tenofovir alafenamide or dolutegravir is required.
Raltegravir	Interaction not studied. <i>Expected:</i> ↔ Tenofovir alafenamide ↔ Raltegravir	No dose adjustment of Tenofovir alafenamide or raltegravir is required.
HIV ANTIRETROVIRAL AGENTS – NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		

Medicinal product by therapeutic areas	Effects on drug levels.	Recommendation concerning co-administration with Tenofovir alafenamide
Efavirenz (600 mg orally, q.d.) Tenofovir alafenamide ^f (40 mg orally, q.d.)	<i>Tenofovir alafenamide</i> ↓ C _{max} ↔ AUC <i>Tenofovir</i> ↓ C _{max} ↔ AUC ↔ C _{min} <i>Expected:</i> ↔ Efavirenz	No dose adjustment of Tenofovir alafenamide or efavirenz is required.
Nevirapine	Interaction not studied. <i>Expected:</i> ↔ Tenofovir alafenamide ↔ Nevirapine	No dose adjustment of Tenofovir alafenamide or nevirapine is required.
Rilpivirine (25 mg orally, q.d.) Tenofovir alafenamide (25 mg orally, q.d.)	<i>Tenofovir alafenamide</i> ↔ C _{max} ↔ AUC <i>Tenofovir</i> ↔ C _{max} ↔ AUC ↔ C _{min} <i>Rilpivirine</i> ↔ C _{max} ↔ AUC ↔ C _{min}	No dose adjustment of Tenofovir alafenamide or rilpivirine is required.
HIV ANTIRETROVIRAL AGENTS – CCR5 RECEPTOR ANTAGONIST		
Maraviroc	Interaction not studied. <i>Expected:</i> ↔ Tenofovir alafenamide ↔ Maraviroc	No dose adjustment of Tenofovir alafenamide or maraviroc is required.
HERBAL SUPPLEMENTS		
St. John's wort (<i>Hypericum perforatum</i>)	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
ORAL CONTRACEPTIVES		
	<i>Norelgestromin</i> ↔ C _{max}	

Medicinal product by therapeutic areas	Effects on drug levels.	Recommendation concerning co-administration with Tenofovir alafenamide
Norgestimate (0.180 mg/0.215 mg/ 0.250 mg orally, q.d.) Ethinyl estradiol (0.025 mg orally, q.d.) Tenofovir alafenamide ^a (25 mg orally, q.d.)	↔ AUC ↔ C _{min} <i>Norgestrel</i> ↔ C _{max} ↔ AUC ↔ C _{min} <i>Ethinyl estradiol</i> ↔ C _{max} ↔ AUC ↔ C _{min}	No dose adjustment of Tenofovir alafenamide or norgestimate/ethinyl estradiol is required.

a. Used as Emtricitabine/tenofovir alafenamide fixed-dose combination tablet

b. A sensitive CYP3A4 substrate

c. Used as Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet

d. Used as Emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet

e. The predominant circulating nucleoside metabolite of sofosbuvir

f. Used as Tenofovir alafenamide 40 mg and emtricitabine 200 mg

g. Used with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV infected patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women exposed to tenofovir alafenamide (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

The use of tenofovir alafenamide may be considered during pregnancy, if necessary.

Breast-feeding

Based on published data, tenofovir alafenamide and tenofovir are excreted in human milk at low levels in women administered with tenofovir alafenamide. 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.

4.7 Effects on ability to drive and use machines

Tenofovir alafenamide may have minor influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with tenofovir alafenamide.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were headache, nausea, and fatigue.

Tabulated summary of adverse reactions

The following adverse reactions have been identified with tenofovir alafenamide in patients with CHB (Table 2). The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) or uncommon ($\geq 1/1,000$ to $< 1/100$).

Table 2: Adverse Reactions Identified with Tenofovir Alafenamide

<i>System organ class</i>	
Frequency	Adverse reaction
<i>Nervous system disorders</i>	
Very common	Headache
Common	Dizziness
<i>Gastrointestinal disorders</i>	
Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
<i>Hepatobiliary disorders</i>	
Common	Increased ALT
<i>Skin and subcutaneous tissue disorders</i>	
Common	Rash, pruritus
Uncommon	Angioedema ¹ , urticaria ¹
<i>Musculoskeletal and connective tissue disorders</i>	
Common	Arthralgia
<i>General disorders and administration site conditions</i>	
Common	Fatigue

¹ Adverse reaction identified through post-marketing surveillance for tenofovir alafenamide-containing

products.

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 drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my (Consumers → Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI))

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: J05AF13.

Mechanism of action

Tenofovir alafenamide is a phosphoramidate 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 pharmacologically 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 HBV and HIV (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.

Antiviral activity

The antiviral activity of tenofovir alafenamide was assessed in HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC₅₀ (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC₅₀ of 86.6 nM. The CC₅₀ (50% cytotoxicity concentration) in HepG2 cells was > 44,400 nM.

Resistance

No amino acid substitutions associated with resistance to Tenofovir alafenamide were identified in these isolates (genotypic and phenotypic analyses) .

Cross-resistance

The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing nucleos(t)ide reverse transcriptase inhibitor mutations in HepG2 cells. HBV isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with resistance to lamivudine remained susceptible to tenofovir alafenamide (< 2-fold change in EC₅₀). HBV isolates expressing the rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir remained susceptible to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir remained susceptible to tenofovir alafenamide; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to tenofovir alafenamide (3.7-fold change in EC₅₀). The clinical relevance of these substitutions is not known.

5.2 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. In patients with CHB, mean steady state AUC₀₋₂₄ for tenofovir alafenamide and tenofovir were 0.22 µg•hr/mL and 0.32 µg•hr/mL, respectively. Steady state C_{max} for tenofovir alafenamide and tenofovir were 0.18 and 0.02 µg/mL, respectively. 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 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. It is shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by carboxylesterase-1 in hepatocytes; and by cathepsin A in peripheral blood mononuclear cells (PBMCs) and macrophages. Tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate.

Tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4.

Elimination

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose

eliminated in urine. Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is renally eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

Linearity/non-linearity

Tenofovir alafenamide exposures are dose proportional over the dose range of 8 to 125 mg.

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 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.

Renal impairment

No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl > 15 but < 30 mL/min).

Paediatric population

No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between adolescent and adult HIV-1 infected subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Magnesium Stearate

Film coat

Polyvinyl Alcohol, Polyethylene Glycol, Titanium Dioxide & Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place below 30°C. Store in the original container

6.4 Nature and contents of container

HDPE Bottle of 30's pack

6.5 Special precautions for disposal

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PRODUCT REGISTRATION HOLDER

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