PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

NEFORIM film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg tenofovir disoproxil fumarate (TDF) equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir, 300 mg lamivudine and 50 mg dolutegravir (as sodium).

Each film-coated tablet contains 68 mg lactose, 125 mg of mannitol and 5,981 mg of sodium.

For full list of excipients, see section 6.1

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (see section 4.4). NEFORIM IS NOT INDICATED FOR TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. THE SAFETY AND EFFICACY OF NEFORIM HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED THE COMBINATION TABLET. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE

CO-INFECTED WITH HIV AND HBV AND WHO DISCONTINUED THE COMBINATION TABLET. IF APPROPRIATE, INITIATION OF ANTI-HEPTATITIS B THERAPY MAY BE WARRANTED (see section 4.4).

3 PHARMACEUTICAL FORM

White to off white capsule shaped, biconvex, film-coated tablets debossed with 'TLD' on one side and break-line on the other side.

The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NEFORIM is indicated for the treatment of HIV-1 infection in adults aged 18 years and older.

4.2 Posology and method of administration

NEFORIM therapy should be initiated by a medical practitioner experienced in the management of human immunodeficiency virus (HIV) infection.

Posology

Adults: The dose of NEFORIM is one tablet taken orally, once daily.

Paediatrics: NEFORIM is not recommended for use in patients younger than 18 years of age.

Special populations

Dose adjustment for renal impairment

Significantly increased exposure occurred when tenofovir, as in NEFORIM, was administered to patients with moderate to severe renal impairment (see section

4.3)

The pharmacokinetics of tenofovir, as in NEFORIM, have not been evaluated in non-haemodialysis patients with creatinine clearance < 50 m/min; therefore, no dosing recommendations is available for these patients.

NEFORIM is not suitable for use in patients with renal impairment with creatinine clearance less than 50 ml/min.

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking NEFORIM.

Method of administration

Oral use.

It is recommended that NEFORIM be swallowed with water, with or without food.

4.3 Contraindications

- NEFORIM is contraindicated in patients with known hypersensitivity to dolutegravir, lamivudine, tenofovir disoproxil fumarate or to any of the excipients of NEFORIM (see section 6.1).
- Uncontrolled renal failure (see section 4.4).
- Pregnancy and lactation (see section 4.6).
- Women of child-bearing age not using highly effective contraception.
- Concomitant use with adefovir dipivoxil.
- Co-administration with dofetilide and pilsicainide.
- Co-administration with didanosine.
- Co-administration with metformin.
- Patients younger than 18 years of age.
- Moderate and severe hepatic impairment.

4.4 Special warnings and precautions for use

Safety and efficacy of the individual active ingredients in various antiretroviral combination regimens with similar dosages as contained in NEFORIM have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination as in NEFORIM for the treatment of HIV have not been established in clinical studies.

The complete patient information leaflets of the other medicines used in combination should be consulted before initiation of therapy.

Metabolic abnormalities

Combination antiretroviral therapy, including NEFORIM has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Lipodystrophy

Combination antiretroviral therapy, including NEFORIM, has also been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting and breast enlargement in HIV patients.

A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Fasting serum lipids and blood glucose levels should be monitored. Lipid disorders should be managed as clinically appropriate. Patients with evidence of lipodystrophy should also have a thorough cardiovascular risk assessment.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, atypical mycobacterial infections, cytomegalovirus retinitis, pneumocystis jirovecii, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued, and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease, Guillain-Barre Syndrome, polymyositis) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART), including components of NEFORIM. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness, or difficulty in movement.

Opportunistic infections

Patients receiving NEFORIM may continue to develop opportunistic infections and other complications of HIV infection and therefore should remain under close clinical observation by doctors experienced in the treatment of patients with HIV associated diseases.

The risk of HIV transmission to others

Patients must be advised that treatment with NEFORIM, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis, usually associated with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, such as in NEFORIM. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure.

Lactic acidosis generally occurs after a few or several months of treatment. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Suspicious biochemical features include mild raised transaminases, raised lactate

dehydrogenase (LDH) and/or creatine kinase. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and respond as follows:

- Lactate 2 - 5 mmol/L: monitor regularly and be alert for clinical signs.
- Lactate 5 - 10 mmol/L without symptoms: monitor closely.
- Lactate 5 - 10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality in case studies).

The above lactate values may not be applicable to paediatric patients.

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with a raised lactate level.

Lactic acidosis and sever hepatomegaly with steatosis, including fatal cases, have been reported with the use of NEFORIM alone or in combination, in the treatment of HIV infection. Most cases were women.

Caution should be exercised when administering NEFORIM to patients with known risk factors for liver disease.

Treatment with NEFORIM should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity. Caution should be exercised when administering nucleoside analogues as contained in NEFORIM to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicines and alcohol). Patients co-infected with

hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk. Patients at increased risk should be followed closely. However, cases have also been reported in patients with no known risk factors.

Patients at increased risk should be followed closely.

There are no study results demonstrating the effect of NEFORIM on clinical progression of HIV-1.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues as contained in NEFORIM have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipidaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving lamivudine, as in NEFORIM. It is unclear whether this is due to lamivudine or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of NEFORIM until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of NEFORIM is increased due to decreased clearance. The dose of NEFORIM should therefore be adjusted (see section 4.2).

Liver disease

Use of NEFORIM can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis).

The safety and efficacy of NEFORIM has not been established in patients with significant underlying liver disorders. Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal impairment

NEFORIM is a combination medicine and the dose of the individual components cannot be altered. Tenofovir and lamivudine are principally eliminated by the kidney. NEFORIM is not recommended for patients with creatinine clearance < 50 ml/min or patients who require haemodialysis. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) has been reported with the use of tenofovir disoproxil fumarate in clinical practice. Careful monitoring of renal function (serum creatinine and serum phosphate) is therefore recommended before taking NEFORIM.

Renal function

Since NEFORIM is primarily eliminated by the kidneys, co-administration of

NEFORIM with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of NEFORIM and/or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.

Renal safety with tenofovir has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 ml/min).

Renal monitoring

It is recommended that renal function (creatinine clearance and serum phosphate) must be assessed in all patients prior to initiating therapy with tenofovir disoproxil fumarate and that it is also monitored every four weeks during the first year of tenofovir disoproxil fumarate therapy, and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

Co-administration and risk of renal toxicity

Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicine (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic medicines is unavoidable, renal function should be monitored weekly.

Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicines which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicine). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and

cidofovir. Consequently, the pharmacokinetics of these medicines, which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4, might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicines which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly.

NEFORIM should be avoided with concurrent or recent use of a nephrotoxic medicine. Patients at risk of, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic substances should be carefully monitored for changes in serum creatinine and phosphorus.

K65R mutation

NEFORIM should be avoided in antiretroviral experienced patients with HIV-1 harbouring the K65R mutation.

Bone mineral density

Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as contained in NEFORIM. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia.

NEFORIM may cause a reduction in bone mineral density. The effects of tenofovir disoproxil fumarate-associated changes in bone mineral density on long-term bone health and future fracture risk are currently unknown.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the

effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

Patients with HIV and hepatitis B or C virus co-infection

NEFORIM is not indicated for the treatment of chronic HBV infection. The safety and efficacy of NEFORIM has not been established for the treatment of patients co-infected with HBV and HIV.

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines.

Patients with chronic hepatitis B or C treated with NEFORIM are at an increased risk for severe and potentially fatal hepatic adverse reactions. Doctors should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

Exacerbations of hepatitis

Flares on treatment

Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum 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 exacerbations of hepatitis have been reported in patients after the discontinuation of 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, have been reported. 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. 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.

Hypersensitivity reactions

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue NEFORIM and other suspect medicines immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with NEFORIM or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction.

Excipients

NEFORIM contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption should not take NEFORIM. Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

Each tablet also contains 5,981 mg of sodium which is less than 1 mmol sodium (23 mg) per tablet, essentially sodium-free.

Paediatric population

Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.

Use in the elderly

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

4.5 Interaction with other medicines and other forms of interaction

The likelihood of interactions is low due to the limited metabolism as plasma protein binding and almost complete renal clearance. Zidovudine plasma levels are not significantly altered when co-administered with lamivudine. Zidovudine has no effect on the pharmacokinetics of lamivudine. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

As NEFORIM contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with NEFORIM. The medicine interactions described are based on studies

conducted with tenofovir disoproxil fumarate or lamivudine as individual medicines or are potential medicine interactions. While the tables include potentially significant interactions, they are not all inclusive. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450-mediated interactions involving tenofovir with other medicines is low.

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in lamivudine plasma levels. This does not require dose adjustment unless the patient also has renal impairment. Administration of co- trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.

Tenofovir

Renally eliminated medicines

Tenofovir, as in NEFORIM, is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of NEFORIM with medicines that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered medicines due to competition for this elimination pathway. Medicines that decrease renal function may also increase serum concentrations of tenofovir, as in NEFORIM.

When administered with multiple doses of tenofovir, the C_{max} and AUC of didanosine 400 mg increase significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules are administered with tenofovir, systemic exposures to didanosine are similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Lamivudine

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance. Zidovudine plasma levels are not significantly altered when co-administered with NEFORIM. Zidovudine has no effect on the pharmacokinetics of NEFORIM.

NEFORIM may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. NEFORIM is therefore not recommended to be used in combination with zalcitabine.

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in NEFORIM plasma levels. Unless the patient has renal impairment, no dosage adjustment of NEFORIM is necessary. NEFORIM has no effect on the pharmacokinetics of co-trimoxazole.
The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route is renal.

The co-administration of NEFORIM with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV + RTV).

Dolutegravir

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given NEFORIM.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in NEFORIM.

Effects of NEFORIM on the pharmacokinetics of other medicines

In vitro, dolutegravir demonstrated no direct, or weak inhibition of the enzyme cytochrome P450, uridine diphosphate glucuronosyl transferase or the transporters Pgp.

In vitro, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4, *in vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Therefore, dolutegravir in NEFORIM is not expected to affect the pharmacokinetics of medicines that are substrates of the these enzymes or transporters (i.e. reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals (such as fluconazole, itraconazole, clotrimazole), proton pump inhibitors (such as esomeprazole, lansoprazole, omeprazole), anti-erectile dysfunction medicines (such as sildenafil, tadalafil, vardenafil), acyclovir, valaciclovir, sitagliptin, adefovir).

Dolutegravir as in NEFORIM do not have any clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibits the renal organic cation transporters 2 (OCT2). Based on this, NEFORIM may increase plasma concentrations of medicines in which excretion is dependent on OCT2 (dofetilide, metformin).

Effects of other medicines on the pharmacokinetics of dolutegravir as in NEFORIM

Dolutegravir as in NEFORIM is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp and BCRP; therefore, medicines that induce those enzymes may theoretically decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir in NEFORIM.

Co-administration of NEFORIM and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration.

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduces the plasma concentrations of dolutegravir significantly and requires dolutegravir dose adjustment of 50 mg twice daily. Etravirine also reduces plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore, no dose adjustment is necessary when co-administered with etravirine. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment. Caution is warranted, and clinical monitoring is recommended when these combinations are given in INI-resistant patients. A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, bocepravir, telaprevir, prednisone, rifabutin and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dose adjustment of dolutegravir is required when co-administered with these medicines.

Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter. Dofetilide or pilsicainide co-administration with NEFORIM is contraindicated due to the potential life- threatening toxicity caused by high dofetilide or pilsicainide concentrations (see section 4.3).

Co-administration of antacids containing polyvalent cations (e.g., Mg, Al, Fe or Ca) decreases dolutegravir plasma concentration. NEFORIM should not be co-administered with polyvalent cation-containing antacids. NEFORIM is

recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.3).

Metformin concentrations may be increased by NEFORIM. Metformin is contraindicated in patients taking NEFORIM (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

NEFORIM should not be prescribed in women who plan to become pregnant. Women of child-bearing age should not use NEFORIM unless they are reliably using highly effective contraception. Treatment with NEFORIM should not be initiated without a medically supervised negative pregnancy test. This test should be repeated at frequent intervals during treatment with NEFORIM; and especially in the event that pregnancy is suspected.

Pregnancy

NEFORIM is contraindicated in pregnancy and lactation. Neural tube defects have been noted in an observational study in humans, where dolutegravir-based regiments were used at the time of conception and early pregnancy (see section 4.3).

Tenofovir, dolutegravir and lamivudine were shown to cross the placenta in reproductive toxicity studies in animals. Late onset neurological disorders, including seizures, have been observed in children who have been exposed to nucleoside analogues such as tenofovir and lamivudine, (see Mitochondrial dysfunction under see section 4.4).

Breastfeeding

Mothers breastfeeding their infants should not use NEFORIM. Lamivudine is excreted in human milk at similar concentrations to those found in serum; tenofovir

is excreted in breast milk and it is not known whether dolutegravir is excreted in human milk. The HIV-1-infected mothers must not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

4.7 Effects on ability to drive and use machines

NEFORIM causes dizziness, impaired concentration and/or drowsiness and may affect the ability to drive and use machines. Patients should ensure that they do not engage in driving or using machines until they know how NEFORIM affects them.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions during treatment are lactic acidosis and severe hepatomegaly with steatosis, effects on serum liver biochemistries in patients with hepatitis B or C co-infection, severe acute exacerbation of hepatitis, hypersensitivity reactions, pancreatitis, new onset or worsening renal impairment, hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C, bone effects of tenofovir disoproxil fumarate, fat redistribution and immune reconstitution syndrome.

b. Tabulated summary of adverse reactions

Dolutegravir

MedDRA system organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Less frequent	Hypersensitivity, immune reconstitution syndrome
Psychiatric disorders	Frequent	Insomnia, abnormal dreams, depression

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Less frequent	Suicidal ideation or suicide attempt (particularly in patients with history of depression or psychiatric illness)
Nervous system disorders	Frequent	Headache, dizziness, abnormal dreams
Gastrointestinal disorders	Frequent	Nausea, diarrhoea
	Less frequent	Flatulence, upper abdominal pain, vomiting
	Frequency unknown	Abdominal pain, abdominal discomfort
Hepato-biliary disorders	Frequency unknown	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus
Musculoskeletal and connective tissue disorders	Less frequent	Arthralgia, myalgia
General disorders and administration site conditions	Frequent	Fatigue
Investigations	Frequent	Raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST), raised creatine kinase

Lamivudine

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Neutropenia, anaemia, thrombocytopenia
	Frequency unknown	Pure red cell aplasia
Metabolism and nutrition disorders	Frequent	Hyperlactataemia
	Less frequent	Lactic acidosis, lipodystrophy (redistribution/ accumulation of body fat), usually associated with severe hepatomegaly and hepatic steatosis (see section 4.4)
	Frequency unknown	Hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia
Nervous system disorders	Frequent	Headache, insomnia
	Frequency unknown	Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children exposed *in utero*
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, nasal symptoms
Gastrointestinal disorders	Frequent	Nausea, vomiting, upper abdominal pain or cramps, diarrhoea

MedDRA system organ class	Frequency	Adverse reactions
	Less frequent	Pancreatitis, elevations in serum amylase
Hepato-biliary disorders	Less frequent	Transient elevations in liver enzymes (AST ALT), hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia
	Less frequent	Angioedema
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, muscle disorders
	Less frequent	Rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures
General disorders and administration site conditions	Frequent	Malaise, fever, fatigue
	Frequency unknown	Immune reconstitution syndrome

Tenofovir

MedDRA system organ class	Frequency	
Immune system disorders	Less frequent	Allergic reactions
Metabolism and nutrition disorders	Frequent	Hypophosphataemia, lactic acidosis
	Less frequent	Hypokalaemia
Nervous system disorders	Frequent	Dizziness, headache
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea
Gastrointestinal disorders	Frequent	Anorexia, diarrhoea, vomiting,

MedDRA system organ class	**Frequency**	
		nausea, dyspepsia, flatulence, abdominal pain
	Less frequent	Increased amylase, pancreatitis
Hepato-biliary disorders	Frequent	Increased liver enzymes, hepatitis
	Less frequent	Hepatic steatosis
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Angioedema
Musculoskeletal and connective tissue disorders	Less frequent	Rhabdomyolysis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy
Renal and urinary disorders	Frequent	Renal insufficiency, increased creatinine, proximal renal tubulopathy (including Fanconi syndrome), renal failure, acute tubular necrosis, nephrogenic diabetes insipidus, proteinuria,
	Less frequent	Nephritis (including acute interstitial nephritis)
General disorders and administration site conditions	Frequent	Asthenia, fatigue

c. Description of selected adverse reactions

Serious dolutegravir hypersensitivity reactions

These hypersensitivity reactions have been characterised by rash, constitutional findings, and sometimes organ dysfunction, including liver injury.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

If overdose occurs the patients must be monitored for evidence of toxicity, and standard supportive treatment applied, as necessary.

Dolutegravir

Management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of NEFORIM. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As NEFORIM is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Lamivudine

Limited data are available on the consequences of ingestion of acute overdose in humans. If overdosage occurs the patient should be monitored, and palliative supportive treatment applied as required.

Tenofovir disoproxil fumarate

If overdose occurs the patient must be monitored for evidence of toxicity and palliative supportive treatment be applied, as necessary. Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 – Antimicrobial (Chemotherapeutic) Medicine. Other than antibiotics. Antiviral Medicine.

ATC Code: J05AR27 Antivirals for treatment of HIV infections, combinations.

Dolutegravir

Dolutegravir inhibits HIV integrase by binding to the integrase active sites and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Resistance in vitro

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir have not been observed during HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir integrase substitution observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wildtype subtype B, C and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

Anti-HIV activity against resistant strains: Reverse transcriptase inhibitor- and protease inhibitor-resistant strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wild-type strain.

Integrase inhibitor-resistant HIV-1 strains: Dolutegravir showed anti-HIV activity (susceptibility) with FC< 5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H.

Integrase inhibitor-resistant HIV-2 strains: Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall, the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Resistance in vivo: Integrase inhibitor naïve patients: No integrase inhibitor (INI) resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment – naïve studies.

Effects on renal function: Dolutegravir has no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Lamivudine

Lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI) and is a selective inhibitor of HIV-1 and HIV-2 replication *in-vitro*.

Lamivudine is metabolised intracellularly to the 5'-triphosphate which has intracellular half-life of 16 – 19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA- and DNA-dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy. Lamivudine-resistant HIV-1 mutants are cross-resistant to didanosine and zalcitabine. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

Tenofovir

Tenofovir disoproxil fumarate, is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate and is converted *in vivo* to tenofovir. It is a nucleoside reverse transcriptase inhibitor.

Tenofovir is phosphorylated by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase ɣ.

Medicine resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro* and a K65R mutation in reverse transcriptase have been selected *in vitro* and, in some patients, treated with tenofovir in combination with certain antiretroviral medicines. In treatment naïve patients treated with tenofovir + lamivudine + efavirenz, viral isolates from 17 % patients with virologic failure showed reduced susceptibility to tenofovir.

In treatment-experienced patients, some of the tenofovir-treated patients with virologic failure through week 96 showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Cross-resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognised. The K65R mutation can also be selected by abacavir, didanosine, or zalcitabine and results in reduced susceptibility to these medicines plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate.

Antiviral activity

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 has been assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50 % inhibitory concentration) values for tenofovir were in the range of 0,04 µM – 8,5

μM. In medicine combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0,5 μM to 2,2 μM). The IC_{50} values of tenofovir against HIV-2 ranged from 1,6 μM to 4,9 μM.

5.2 Pharmacokinetic properties

Dolutegravir

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate.

Following single dose administration of Dolutegravir 50 mg tablets in healthy volunteers, the mean (± SD) dolutegravir C_{max} was 2 467 ng/ml (± 665) and the mean (SD) AUC_{0-inf} was 53704 ng.hour/ml (± 18 795) and AUC_{0-t} was 50 692 ng.hour/ml (±16 877). The mean (± SD) dolutegravir t_{max} was 2,45 (± 1,29) hours.

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablets, dolutegravir exhibited non-linear pharmacokinetics with less than dose- proportional increases in plasma exposure from 2 to 100 mg; however, increase in dolutegravir exposure appears dose-dependent from 25 to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg once daily.

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max} and C_{24} h ranging from 1,2 – 1,5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a P-gp substrate *in vitro.* The absolute bioavailability of dolutegravir has not been established.

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increased dolutegravir AUC (0 – ∞) by 33 %, 41 % and 66 %, increased C_{max} by 46 %, 52 % and 67 % and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.

Distribution

Dolutegravir is highly bound (≥ [>] 98.9 %) to human plasma proteins based on *in vitro* data. The apparent volume of distribution following 50 mg once daily administration is estimated at 17 to 20 litres in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0,441 to 0,535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is estimated at approximately 0,2 – 1,1 % in healthy subjects with moderate hepatic impairment and 0,8 – 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients. Dolutegravir is present in cerebrospinal fluid (CSF). In treatment-naïve patients on dolutegravir 50 mg plus abacavir/lamivudine, the median dolutegravir concentration in CSF was

13,2 ng/ml (3,74 ng/ml – 18,3 ng/ml) 2 to 6 hours post-dose after 16 weeks of treatment.

Biotransformation

Dolutegravir is primarily metabolised through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma Of the total oral dose, 53 % is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen.

Excretion in the urine accounts for 31[~~3~~] % of the total oral dose as ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose). Renal elimination of unchanged drug was low (< 1 % of the dose).

Elimination

Dolutegravir has a terminal half-life of about 14 hours and an apparent oral clearance (CL/F) of 1,0 L per hour based on population pharmacokinetic analyses.

Special populations

Children

The pharmacokinetics of dolutegravir in antiretroviral treatment-experienced HIV-1 infected adolescents (12 up to 18 years of age) showed that a dose of dolutegravir 50 mg once daily resulted in dolutegravir exposure comparable to that in adults who received a dose of 50 mg once daily.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir

exposure.

Renal impairment

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. There are no clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 ml/min) and matching healthy subjects. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in metabolising enzymes

There is no evidence that common polymorphisms in metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent.

Gender

Population PK analyses using pooled pharmacokinetic data from adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

Race

Population PK analyses using pooled pharmacokinetic data from adult trials revealed no clinically relevant effect of race on the exposure of dolutegravir.

Co-infection with hepatitis B or C

Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on subjects with hepatitis B co-infection.

Lamivudine

Absorption

Lamivudine is rapidly absorbed and extensively distributed following oral administration. Bioavailability in adult subjects is 86 % ± 16 % (mean ± SD) for the 150-mg tablet. The area under the plasma concentration versus time curve (AUC) and C_{max} increases in proportion to oral dose over the range from 0,25 to 10 mg per kg. The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1,50 following 15 days of oral administration of 2 mg per kg twice daily. The mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour

Effects of food on oral absorption

Lamivudine may be administered with or without food.

Absorption of lamivudine was slower in the fed state (T_{max}: 3,2 ± 1,3 hours) compared with the fasted state (T_{max}: 0,9 ± 0,3 hours); C_{max} in the fed state was 40 % ± 23 % (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasted states.

Distribution

Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1,3 ± 0,4 L/kg suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (less than 36 %). *In vitro* studies showed that over the concentration range of 0,1 to 100 µg/ml, the amount of lamivudine associated with erythrocytes ranged from 53 % to 57 % and was independent of concentration.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range

Metabolism

Metabolism of lamivudine is a minor route of elimination._In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite (approximately 5 % of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined. Lamivudine is not significantly metabolized by CYP450 enzymes.

Elimination

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was 199,7 ± 56,9 ml/min (mean ± SD). In HIV-1-infected subjects given a single IV dose, renal clearance was 280,4 ± 75,2 ml/min (mean ± SD), representing 71 % ± 16 % (mean ± SD) of total clearance of lamivudine. In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398,5 ± 69,1 ml/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0,25 to 10 mg per kg.

No dose adjustment is needed when co-administered with food as lamivudine bioavailability is not altered, although a delay in T_{max} and reduction in C_{max} have been observed. Lamivudine exhibits linear pharmacokinetics over the therapeutic

dose range and displays limited binding to the major plasma protein albumin. Lamivudine elimination will be affected by renal impairment.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary. The likelihood of adverse drug interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance. An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patients also has renal impairment. Administration of cotrimoxazole with the 3TC/zidovudine combination in patients with renal impairment should be carefully assessed. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2 – 4 hours after oral administration is approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Special populations

Children

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55 – 65 %) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age approaching adult values around 12 years of age. Recent findings indicate that exposure in children 2 to < 6 years of age may be reduced by about 30 % compared with other pharmacokinetic data for patients < 3 months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely due to immature renal function and variable absorption.

Pregnancy

Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant adults. Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia. Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenic assay.

Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 30 – 40 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment. There is as yet no information on the tumorigenic risk in animals, and therefore any potential risk to humans must be balanced against the expected benefits of treatment.

Renal impairment

Studies in patients with renal impairment show that lamivudine elimination is affected by renal dysfunction. Dose reduction is recommended for patients with creatinine clearance ≤ 50 ml/min (see section 4.2).

Tenofovir disoproxil fumarate

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil

fumarate in fasted patients is approximately 25 %. Following oral administration of 300 mg tenofovir disoproxil to HIV infected patients in the fasted state, maximum serum concentration (C_{max}) were achieved in 1,0 ± 0,4 hrs (mean ± SD), and C_{max} and AUC values are 0,30 ± 0,09 µg/ml and 2,29 ± 0,69 µg•hr/ml, respectively. The pharmacokinetics of tenofovir are dose proportional over a dose range of 75 to 600 mg and are not affected by repeated dosing

Effects of Food on Oral Absorption

Administration of tenofovir following a high-fat meal (~700 to 1000 kcal containing 40 % to 50 % fat) increases the oral bioavailability, with an increase in tenofovir AUC0-∞ of approximately 40 % and an increase in C_{max} of approximately 14 %. However, administration of tenofovir with a light meal does not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 0,33 ± 0,12 µg/ml and 3,32 ± 1,37 µg•hr/ml following multiple doses of tenofovir disoproxil 300 mg once daily in the fed state, when meal content was not controlled.

Distribution

In vitro protein binding of tenofovir to plasma or serum protein was less than 0,7 and 7,2 %, respectively, over the tenofovir concentration range 0,01 to 25,0 µg/ml.

The volume of distribution at steady-state is 1,3 ± 0,6 l/kg and 1,2 ± 0,4 l/kg, following intravenous administration of tenofovir 1,0 mg/kg and 3,0 mg/kg.

Metabolism

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes. Following IV administration of tenofovir,

approximately 70 – 80 % of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir 300 mg once daily (under fed conditions), 32 ± 10 % of the administered dose is recovered in urine over 24 hours.

Elimination

Tenofovir is primarily excreted by the kidney, both by glomerular filtration and [~~an~~] active tubular transport secretion There may be competition for elimination with other compounds that are also renally eliminated.

Special populations

Age and gender

Pharmacokinetic studies have not been performed in children or in the elderly (over 65 years). Pharmacokinetics have not been specifically studied in different ethnic groups.

Renal impairment

Tenofovir pharmacokinetics are altered in patients with renal impairment.

In patients with creatinine clearance < 50 ml/min or with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, Cmax and AUC-∞ of tenofovir were increased. It is recommended that the dosing interval for tenofovir disoproxil is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2). Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a four-hour haemodialysis session removed approximately 10 % of the administered dose

Hepatic impairment

When a single dose of tenofovir disoproxil was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification, the tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment, suggesting that no dose adjustment is required in these subjects.

Intracellular pharmacokinetics

Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs).

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Colloidal silicon dioxide

Croscarmellose sodium

Crospovidone

Lactose

Magnesium stearate

Mannitol (E421)

Microcrystalline cellulose

Povidone

Pregelatinised starch

Sodium starch glycolate

Sodium stearyl fumarate

Film-coat

Macrogol/PEG

Polyvinyl alcohol (partly hydrolysed)

Talc

Titanium dioxide (E171)

6.2 Incompatibilities

None.

6.3 Shelf life

24 months

Unused tablets should be discarded 90 days after first opening of the bottle. When the bottle is first opened this “Date of opening” should be written on the bottle label in the place provided. (This is only applicable to pack size of 90 tablets).

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

28 or 30 tablets packed in 100 ml white opaque HDPE container closed with 38 mm white opaque polypropylene ribbed screw cap with liner.

56 or 60 tablets packed in 150 ml white opaque HDPE container closed with 38 mm white opaque polypropylene ribbed screw cap with liner.

84 or 90 tablets packed in 250 ml white opaque HDPE container closed with 53 mm white opaque polypropylene ribbed screw cap with liner.

All pack sizes contain a 3 g molecular sieve canister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma (SA) Pty Ltd

106 16th Road

Building 2

Midrand

Email: pv@trinitypharma.co.za

Contact number: +27 (0)10 594 5610

8 REGISTRATION NUMBER(S)

NEFORIM: 530310

LENDOFIL: 530311.310

VIDAVIR: 530312.310

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To follow

10 DATE OF REVISION OF THE TEXT

18 November 2025