PROFESSIONAL INFORMATION LEAFLET

SCHEDULING STATUS: **S4**

1. NAME OF MEDICINE

TLADEEZ (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TLADEEZ film-coated tablet contains:

Lamivudine	300 mg
Tenofovir disoproxil fumarate	300 mg
Dolutegravir sodium equivalent to	
Dolutegravir	50 mg

Contains sugar (lactose monohydrate 136 mg) and sweetener (mannitol 131,4 mg).

For full list of excipients, see section 6.1.

WARNING:

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 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

TLADEEZ IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. SAFETY AND EFFICACY OF TLADEEZ 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 DISCONTINUE TLADEEZ AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE *SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

3. PHARMACEUTICAL PRESENTATION

White to off white, film-coated, capsule-shaped, biconvex bevelled edge tablet debossed with “M” on one side and “LTD” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

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

4.2. Posology and method of administration

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Adults:

The dose of TLADEEZ is one tablet taken orally, once daily, without regard to food.

Paediatrics:

TLADEEZ is not recommended for use in patient's younger than 18 years of age.

Renal impairment:

Significantly increased exposure occurred when tenofovir, as in TLADEEZ**,** was administered to patients with renal impairment (see *Contraindications*).

The pharmacokinetics of tenofovir, as in TLADEEZ, have not been evaluated in non-haemodialysis patients with creatinine clearance < 80 mL/min); therefore, no dosing recommendations are available or possible with this combination for these patients.

TLADEEZ is contraindicated in patients with renal impairment with creatinine clearance less than 80 mL/min.

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir 50 mg should be given to patients taking TLADEEZ.

The combined use of isoniazid and dolutegravir, as in TLADEEZ, may result in unexpected toxicity due to endogenous cytokine release. Co-administration is not recommended unless futher investigations are performed.

4.3. Contraindications

TLADEEZ tablets are contraindicated in patients with:

- known hypersensitivity to lamivudine, tenofovir or dolutegravir or to any of the components of the tablets.
- impaired renal failure.
- pregnancy and lactation (see *Fertility, pregnancy, and lactation*).
- 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 TLADEEZ have been

established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed drug combination as in TLADEEZ for the treatment of HIV have not been established in clinical studies.

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

Metabolic abnormalities

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

Lipodystrophy:

Combination antiretroviral therapy, including TLADEEZ, 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.

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 / Immune Reactivation Syndrome:

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. This 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. Typically, such reactions have been observed within the first few weeks or months of initiation of combination Anti-Retroviral Therapy (cART). Such reactions typically present with 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, generalised and/or focal mycobacterial infections, including atypical mycobacterial infections, cytomegalovirus retinitis, *Pneumocystis jerovecii (carinii)* and cryptococcal meningitis. Any inflammatory symptoms should be evaluated, and 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 TLADEEZ. 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 TLADEEZ 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 antiretroviral TLADEEZ, have 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 TLADEEZ. 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, hyperthyroidism, 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 severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of TLADEEZ alone or in combination, in the treatment of HIV infection. Most cases were women.

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

Treatment with TLADEEZ 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 TLADEEZ 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 TLADEEZ on clinical progression of HIV-1.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues as contained in TLADEEZ 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 TLADEEZ. 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 TLADEEZ until diagnosis of pancreatitis is excluded.

Patients with renal impairment:

In patients with renal impairment, the terminal half-life of TLADEEZ is increased due to decreased clearance (see *Contraindications).*

Liver disease:

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

The safety and efficacy of TLADEEZ 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:

TLADEEZ is a combination product, and the dose of the individual components cannot be altered. Tenofovir and lamivudine are principally eliminated by the kidney. TLADEEZ is not recommended for patients with creatinine clearance < 80 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 TLADEEZ.

Renal function:

Since TLADEEZ is primarily eliminated by the kidneys, co-administration of TLADEEZ with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of TLADEEZ 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) is 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 for changes in serum creatinine and phosphorus.

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.

K65R mutation:

TLADEEZ 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 TLADEEZ. 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.

TLADEEZ 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:

TLADEEZ is not indicated for the treatment of chronic HBV infection. The safety and efficacy of TLADEEZ 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 such as TLADEEZ 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.

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 dolutegravir, and were characterized by rash, constitutional findings and sometimes, organ dysfunction, including severe liver reactions. TLADEEZ should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect active

substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Paediatric use:

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 patients aged 65 and over to determine whether they respond differently from younger patients.

Important information about some of the ingredients of TLADEEZ:

TLADEEZ contains lactose. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take TLADEEZ.

TLADEEZ tablets contains mannitol and may have a laxative effect.

TLADEEZ contains lactose and mannitol which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5. Interaction with other medicines and other forms of interaction

There have been no medicine interaction studies conducted using TLADEEZ.

TLADEEZ contains tenofovir, lamivudine and dolutegravir. Interactions that have been identified with these individual medicines may occur with TLADEEZ.

Lamivudine:

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, as in TLADEEZ. Zidovudine has no effect on the pharmacokinetics of lamivudine as in TLADEEZ. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine, as in TLADEEZ, is therefore not recommended to be used in combination with zalcitabine.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposed at therapeutic doses. 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. Lamivudine, as in TLADEEZ, 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.

Other medicines that are eliminated only in part by this route, such as cimetidine and ranitidine, were shown not to interact with lamivudine, as in TLADEEZ, hence no dosage adjustments are required.

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

Pharmacokinetic parameters (Mean ± SD) after a single 300 mg Oral dose of Lamivudine in 3 groups of adults with varying degrees of Renal Function

Parameters	**Creatinine Clearance Criterion (Number of Subjects)**		
	>60 mL/min (n = 6)	**10 – 30 mL/min (n = 4)**	**<10 mL/min (n=6)**
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2,6 ± 0,5	3,6 ± 0,8	5,8 ± 1,2
AUC∞ (mcg/mL)	11,0 ± 1,7	48,0 ± 19	157 ± 74
C1/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Pharmacokinetic Parameters (Geometric Mean [95 % CI]) after Repeat Dosing of Lamivudine in 3 Paediatric Trials

	Trial (Number of Subjects)					
	ARROW PK (n = 35)		**PENTA-13 (n = 19)**		**PENTA-15 (n = 17)[a]**	
Age Range	**3 – 12 years**		**2 – 12 years**		**3 – 36 months**	
Formulation	**Tablet**		**Solution and Tablet[b]**		**Solution**	
Parameter	**Once daily**	**Twice daily**	**Once daily**	**Twice daily**	**Once daily**	**Twice daily**

C_{max} (mcg/mL)	3,17 (2,76; 3,64)	1,80 (1,59; 2,04)	2,09 (1,80; 2,42)	1,11 (0,96; 1,29)	1,87 (1,65; 2,13)	1,05 (0,88; 1,26)
$AUC^{(0-24)}$ (mcg•mL)	13,0 (11,4; 14,9)	12,0 (10,7; 13,4)	9,80 (8,64; 11,1)	8,88 (7,67; 10,3)	8,66 (7,46; 10,1)	9,48 (7,89; 11,4)

Tenofovir:

No medicine interaction studies have been conducted using TLADEEZ. As TLADEEZ contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with TLADEEZ. Important medicine interaction information for TLADEEZ is summarised in Tables 1 and 2. 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 medicinal products is low.

Renally eliminated medicines:

Tenofovir, as in TLADEEZ, is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of TLADEEZ 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 TLADEEZ.

Tenofovir has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives, and ribavirin. Tables 1 and 2 summarise pharmacokinetic effects of co-administered medicine on tenofovir pharmacokinetics and effects of tenofovir on the pharmacokinetics of co-administered medicine.

When administered with multiple doses of tenofovir, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown.

When didanosine 250 mg enteric-coated capsules were administered with tenofovir, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 1:

Medicine Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of Co-Administered Medicines:

Co-administered Medicine	**Dose of Co-Administered Medicine (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[2] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	⇔	⇔	NC

Adefovir dipivoxil	10 once	22	⇔	⇔	⇔
Atazanavir	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)

1. Patients received tenofovir as tenofovir DF 300 mg once daily
2. Increase =↑; Decrease = ↓; No effect = ⇔; NC = Not calculated

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy, oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant medicine interactions between these agents and tenofovir disoproxil fumarate.

There were no clinically significant pharmacokinetic interactions when tenofovir was co-administered with saquinavir (ritonavir boosted).

Table 2:

Medicine Interactions: Changes in Pharmacokinetic Parameters for Co-Administered Medicines in the Presence of Tenofovir

Co-administered Medicine	**Dose of Co-Administered Medicine (mg)**	**N**	**% Change of Co-administered Medicine Pharmacokinetic Parameters[1] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑ 122 (↑ 1 to ↑ 26)	⇔	NA
Adefovir dipivoxil	10 once	22	⇔	⇔	NA
Efavirenz	600 mg once daily x 14 days	30	⇔	⇔	⇔

Emtricitabine	200 mg once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 mg three times daily x 7 days	12	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 mg twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 mg twice daily x 14 days	21	⇔	⇔	⇔
Methadone[2]	40-110 once daily x 14 days[3]	13	⇔	⇔	⇔

Oral contraceptives[4]	Ethinyl oestradiol/ Norgestimate (Ortho-Tricyclen®) Once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Atazanavir[5]	400 once daily x 14 days	29	⇔	⇔	⇔
Atazanavir[5]	Atazanavir/ Ritonavir 300/100 once daily x 42 days	10	↑ 28 (↑ 50 to ↑ 5)	↑ 25 (↑ 42 to ↑ 3)	↑ 23[6] (↑ 46 to ↑ 10)

1. Increase = ↑; Decrease = ↓; No effect = ⇔; NA = Not applicable
2. R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 300 mg
3. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported
4. Ethinyl oestradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir as tenofovir DF 300 mg
5. REYATAZ US Prescribing Information (Bristol-Myers Squibb)

6. In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2,3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone

The co-administration of TLADEEZ 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) (see *Interaction with other medicines and other forms of interaction*).

Dolutegravir:

Table 3: Medicine Interactions

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TLADEEZ or Concomitant Medicine**	**Clinical comment**
HIV-1 Antiviral medicines[1]		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % C_T ↓ 88 % ETR↔	Etravirine decreased dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. TLADEEZ should not be used with etravirine

		without co-administration of atazanavir + ritonavir, darunavir + ritonavir or lopinavir + ritonavir.
Non-nucleoside Reverse Transcriptase inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39% C_T ↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir contained in TLADEEZ is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of

		nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of dolutegravir contained in TLADEEZ is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑91 % C_{max} ↑ 49% C_{τ} ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentrations. No dose adjustment is necessary.
Protease inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 33 % C_{τ} ↑ 121 % ATV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment in necessary.

	RTV ↔	
Protease inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47% C_T↓ 76 % TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir contained in TLADEEZ is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.
Protease inhibitor: Fosamprenavir/ritonavir (FPV + RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24% C_T↓ 49 % FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients.

		Alternative combinations that do not include Fosamprenavir/ritonavir should be used where possible in INI resistant patients.
Protease inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary
Protease inhibitor: Lopinavir/ ritonavir (LPV + RTV)	DTG ↔ AUC ↔ C_{max} ↔ C_{T} ↔ LPV ↔ RTV↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease inhibitor: Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 32 % C_{max} ↓ 11 % C_{T}↓ 38 % DRV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent.

	RTV ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDV)	Dolutegravir ↔ TDV ↔	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑10 % C_{max} ↑7 % C_T ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % C_T↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary
Other medicines		

Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with TLADEEZ is contra-indicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see *Contraindications*).
Oxcarbazepine Phenytoin Phenobarbitone Carbamazepine St. John's wort	Dolutegravir ↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these

		metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cation decreased dolutegravir plasma concentration. TLADEEZ is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	TLADEEZ is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administer with food.
Iron supplements	Dolutegravir ↓ AUC ↓ 54 %	TLADEEZ is recommended to be

	C_{max} ↓ 57 % C_{24} ↓ 56 %	administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contra-indicated in patients taking TLADEEZ (see *Contraindications*)
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_{T}↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir contained in TLADEEZ is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used

		where possible for INI resistant patients.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN)	Effect of dolutegravir EE ↔ AUC ↑3 % C_{max} ↓1 % C_T ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % C_T↓ 7%	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with TLADEEZ.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % C_T ↓ 1%	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with TLADEEZ.

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

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

In vitro, TLADEEZ demonstrated no direct, or weak inhibition (IC_{50} > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT) 1A1 Or UGT2B7, or the transporters Pgp, BCRP, OATP1B3, OCT1 or MRP2.

In vitro, dolutegravir did not include CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, CYP3A4 probe. Based on these data, dolutegrair as in TLADEEZ is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters (e.g., 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 agents (such as sildenafil, tadalafil, vardenafil), acyclovir, valaciclovir, sitagliptin, adefovir).

In interaction studies, TLADEEZ did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, duranavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OTC2). Based on this observation, TLADEEZ may increase plasma concentrations of medicines in which excretion is dependent upon OCTZ (dofetilide, metformin).

TLADEEZ should not be co-administered with polyvalent cation-containing antacids. TLADEEZ is recommended to be administered 2 hours before or 6 hours after these medicines (see *Interaction with other medicines and other forms of interaction*).

Metformin concentrations may be increased by TLADEEZ. Metformin is contra-indicated in patients taking TLADEEZ (see *Contraindications*).

4.6. Fertility, pregnancy and lactation

Tenofovir and Lamivudine

TLADEEZ is contraindicated in pregnancy and lactation.

Tenofovir 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, in utero (see Mitochondrial Dysfunction under *Special warnings and precautions for use*).

TLADEEZ should not be prescribed in women who plan to become pregnant. Woman of child-bearing age should not use TLADEEZ unless they are reliably using highly effect contraception. Treatment with TLADEEZ should not be initiated without a medically supervised negative pregnancy test. This test should be repeated at

frequent intervals during treatment with TLADEEZ; and especially in the event that pregnancy is suspected.

Lactation:

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

Dolutegravir

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of TLADEEZ in women of childbearing potential to exclude inadvertent (unintentional) use of TLADEEZ during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with dolutegravir versus using another antiretroviral regimen should be discussed with her.

Pregnancy

Use of dolutegravir during pregnancy was associated with a small increase in the prevalence of neural tube defects (0.19%) compared to non-dolutegravir regimens

(0.11%). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus. Dolutegravir was shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

Breast-feeding

HIV infected women should not breast-feed their infants in order to avoid transmission of HIV or follow appropriate guidelines.

Dolutegravir is excreted in human breast milk, and there is significant exposure to the neonate/infants due to slow elimination; the half-life of dolutegravir in the new born was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Fertility

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

TLADEEZ may make the patient feel tired, weak, lightheaded, or dizzy 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 TLADEEZ affects them.

4.8. Undesirable effects

TLADEEZ can have side effects.

Lamivudine:

The following side effects have been reported during therapy for HIV disease with TLADEEZ tablets alone and in combination with other antiretrovirals.

Blood and lymphatic system disorders:

Less frequent: neutropenia, anaemia, thrombocytopenia, pure red cell aplasia

Metabolism and nutrition disorders:

Frequent: hyperlactataemia

Less frequent: lactic acidosis, lipodystrophy (redistribution/accumulation of body fat) (see *Warnings and special precautions*)

Psychiatric disorders:

Frequent: insomnia and other sleep disorders; depressive disorders

Nervous system disorders:

Frequent: headache

Less frequent: paraesthesia, peripheral neuropathy has been reported, although a causal relationship to treatment is uncertain, late onset neurological disorders in children exposed *in utero*

Gastrointestinal disorders:

Frequent: nausea, vomiting, upper abdominal pain; diarrhoea, cramps

Less frequent: pancreatitis, although a causal relationship to treatment is uncertain. Rise in serum amylase

Respiratory, thoracic, and mediastinal disorders:

Frequent: cough, nasal symptoms

Hepatobiliary disorders:

Less frequent: transient rises in liver enzymes (AST, ALT), hepatitis

Skin and subcutaneous tissue disorders:

Frequent: rash, alopecia

Musculoskeletal and connective tissue disorders:

Frequent: arthralgia, muscle disorders, musculoskeletal pain

Less frequent: rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures, myalgia, osteonecrosis, myositis

General disorders and administration site conditions:

Frequent: fatigue, malaise, fever

Investigations:

Frequent: absolute neutrophil count < 750/mm^3; reduction in haemoglobin (< 8,0 g/dL); increase in ALT and AST > 5,0 x ULN (upper limit of normal)

Less frequent: reduced platelets (< 50 000/mm^3); increase in bilirubin (> 2,5 x ULN)

<u>Tenofovir disoproxil fumarate:</u>

Immune system disorders:

Less frequent: allergic reaction (including angioedema), immune reconstitution inflammatory syndrome

Metabolism and nutrition disorders:

Frequency unknown: hypophosphataemia, lactic acidosis

Psychiatric disorders:

Frequent: depression, insomnia, anxiety

Nervous system disorders:

Frequent: dizziness, peripheral neuropathy; headache

Respiratory, thoracic, and mediastinal disorders:

Frequency unknown: dyspnoea

Gastrointestinal disorders

Frequency unknown: abdominal pain, anorexia, dyspepsia, flatulence, increased amylase; pancreatitis

Hepatobiliary disorders

Frequency unknown: increased liver enzymes, hepatitis, hepatomegaly, steatosis

Skin and subcutaneous tissue disorders:

Freqency unknown: rash

Musculoskeletal, connective tissue system and bone disorders:

Freqency unknown: myopathy, osteomalacia (both associated with proximal renal tubulopathy

Renal and urinary disorders

Frequency unknown: renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, nephritis

General disorder and administration site disorders:

Frequent: asthenia, fatigue, pain, fever, abdominal pain, back pain

Investigations:

Frequent: increased fasting cholesterol, raised creatinine kinase; rise in serum amylase, increases in AST and ALT, haematuria, decreased neutrophil count, increased fasting triglyceride levels

Dolutegravir:

Immune system disorders:

Less frequent: hypersensitivity, immune reconstitution syndrome

Psychiatric disorders:

Frequent: insomnia, anxiety, depression, paranoia, suicidal ideation

Nervous system disorders:

Frequent: headache, dizziness, abnormal dreams

Ear and labyrinth disorders:

Frequent: vertigo

Gastrointestinal disorders:

Frequent: nausea, diarrhoea, vomiting, flatulence, upper abdominal pain

Less frequent: abdominal pain, abdominal discomfort, gastritis

Hepatobiliary disorders:

Less frequent: hepatitis

Skin and subcutaneous tissue disorders:

Frequent: rash, pruritus

Musculoskeletal, connective tissue and bone disorders:

Less frequent: athralgia, myalgia

Renal and urinary disorders:

Less frequent: renal impairment

General disorders and administration site conditions:

Frequent: fatigue

Investigations:

Frequent: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations, creatine phosphokinase (CPK) elevations raised bilirubin levels, hyperglycaemia, increased lipase levels, decreased neutrophil counts, changes in serum cholesterol and triglyceride levels

4.9. Overdose

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.

Lamivudine:

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

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 TLADEEZ. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As TLADEEZ is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological class

A 20.2.8 Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents.

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

5.1 Pharmacodynamic properties:

Lamivudine:

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

Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an 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 disoproxil fumarate:

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 in DNA, by chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, ß and mitochondrial DNA polymerase Ɣ.

Drug 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 to 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.

Dolutegravir:

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t½ 71 hours).

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 substitutions 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 wildtype 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 patients 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: The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated. A small decrease of 10 - 14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir had 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.

5.2 Pharmacokinetics properties:

TLADEEZ contains a fixed-dose combination of dolutegravir, lamivudine and tenofovir. When administered as a fixed-dose combination, results from the bioequivalence trial have demonstrated that the pharmacokinetic properties of the individual components are not significantly different to those observed when they are administered separately as single entities (as described below).

Lamivudine:

Pharmacokinetics in adults:

Absorption:

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 to 85 %. Following oral administration, the mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels, i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1-1,5 µg/mL.

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.

Distribution:

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.

From intravenous studies, the mean volume of distribution is 1,3 L/kg. Limited data shows lamivudine penetrates to the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2 – 4 hours after oral administration was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Metabolism and elimination:

From intravenous studies, the mean terminal half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/kg/h, with predominantly renal clearance (> 70 %) via active tubular secretion, but little (< 10 %) hepatic metabolism.

Lamivudine elimination will be affected by renal impairment, whether it is disease or age related.

The likelihood of adverse drug interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

Tenofovir disoproxil fumarate:

Absorption:

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir in fasted patients is approximately 25 %. Following oral administration of a single dose of tenofovir 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1,0 ± 0,4 hrs. C_{max} and AUC values are 296 ± 90 ng/mL and 2287 ± 685 ng*h/mL, respectively. The pharmacokinetics of tenofovir are dose proportional over a tenofovir dose range of 75 to 600 mg and are not affected by repeated dosing.

Effects of food on oral absorption:

Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40 % and C_{max} by approximately 14 %. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the substance. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ± 119 ng/mL and 3324 ± 1370 ng*h/mL following multiple doses of tenofovir 300 mg once daily in the fed state, when meal content was not controlled.

Distribution:

In vitro binding of tenofovir to human plasma or serum protein is less than 0,7 % and 7,2 %, respectively, over the tenofovir concentration range 0,01 to 25 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 and elimination:

In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. 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. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations:

Paediatrics and the elderly:

Pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (> 65 years).

Hepatic impairment:

Tenofovir pharmacokinetics after a 300 mg single dose have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. Change in tenofovir dosing is not required in patients with hepatic impairment.

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) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased. It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see *Dosage and directions for use*). 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 tenofovir dose.

Dolutegravir:

Absorption:

Dolutegravir is absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for the tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, 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 proportional from 25 mg to 50 mg. 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 34 %, 41 %, and 66 %, increased C_{max} by 46 %, 52 %, and 67 %, prolonged T_{max} to 3, 4 and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant. The absolute bioavailability of dolutegravir has not been established.

Distribution:

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on *in vitro* data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12,5 L. Binding of dolutegravir to plasma was independent of 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. Dolutegravir is present in cerebrospinal fluid (CSF). Dolutegravir concentrations in CSF exceeded the IC_{50}, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy (see *Pharmacodynamic properties*).

Metabolism:

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 %) of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose).

Elimination:

Dolutegravir has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 0,56 L/hr.

Special patient populations:

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. Pharmacokinetic data for dolutegravir in subjects of > 65 years old are limited.

Renal impairment:

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr < 30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 mL/min) and matching healthy subjects were observed, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 %, and 43 %, respectively, compared with those in matched 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. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B score 7 to 9) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is necessary for patients with

mild 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. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32 % lower clearance of dolutegravir and 46 % higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41). Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Excipients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone (K – 30), sodium starch glycolate (Type A) [film-coating colourant: Opadry II White: macrogol / PEG 4000; polyvinyl alcohol – part. Hydrolysed; talc; titanium dioxide].

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C. Store in the original container. Do not remove from the carton until required for use. Keep the bottle tightly closed.

6.5. Nature and contents of container

TLADEEZ will be packed in a round, white or blue, opaque High-Density Polyethylene (HDPE) bottle, round wide mouth, white or blue opaque polypropylene (PP) screw closure and with wad containing aluminium induction sealing liner. Packed in an outer carton except for 28’s pack size.

Pack sizes of 28’s 30’s, 84’s, 90’s and 180’s.*

* Not all pack sizes may be marketed

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Kiara Health (Pty) Ltd

72 Steel Road

Spartan

Kempton Park

1619

South Africa

8. REGISTRATION NUMBER

52/20.2.8/0945

9. DATE OF FIRST AUTHORISATION

10 October 2018

10. DATE OF REVISION OF THE TEXT

28 October 2022