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 SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

RANEGA IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. SAFETY AND EFFICACY OF RANEGA 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 INFECTED WITH HBV WHO DISCONTINUE RANEGA AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

RANEGA (film-coated tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each RANEGA film-coated tablet contains:

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

Excipients with known effect:

Contains sugar: Lactose monohydrate 136 mg

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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

Adults:

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

Special Populations

Paediatrics:

RANEGA is not recommended for use in patients younger than 18 years of age.

Dose adjustment for renal impairment:

Significantly increased exposure occurred when tenofovir, as in RANEGA , was administered to patients with moderate to severe renal impairment (see section 4.3 Contraindications).

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

RANEGA 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 RANEGA.

4.3 Contraindications

- RANEGA tablets are contraindicated in patients with known hypersensitivity to lamivudine, tenofovir or dolutegravir or to any of the components of the tablets.
- Uncontrolled renal failure (see section 4.4 Special warnings and precautions for use).
- Pregnancy and lactation (see section 4.6 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.
- 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 RANEGA have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed drug combination as in RANEGA for the treatment of HIV have not been established in clinical studies.

Depression (including suicidal ideation):

RANEGA can cause depression and suicidal ideation behaviour, particularly in patients with a pre-existing history of depression or psychiatric illness. Patients should inform their doctor if they notice any symptoms of depression during treatment.

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

Metabolic abnormalities:

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

Lipodystrophy:

Combination antiretroviral therapy, including RANEGA, 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 RANEGA. 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 RANEGA 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 RANEGA, 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 RANEGA. 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 severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of RANEGA alone or in combination, in the treatment of HIV infection. Most cases were women.

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

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

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues as contained in RANEGA 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 RANEGA. 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 RANEGA 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 RANEGA is increased due to decreased clearance. The dose of RANEGA should therefore be adjusted (see section 4.2 Posology and method of administration).

Liver disease:

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

The safety and efficacy of RANEGA 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:

RANEGA is a combination product and the dose of the individual components cannot be altered. Tenofovir and lamivudine are principally eliminated by the kidney. RANEGA 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 RANEGA.

Renal function:

Since RANEGA is primarily eliminated by the kidneys, co-administration of RANEGA with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of RANEGA 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.

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.

RANEGA 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:

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

Bone effects:

Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as contained in RANEGA. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported.

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

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomised controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients (see section 4.8 Undesirable effects). These BMD decreases generally improved after treatment discontinuation.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Overall in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures.

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8 Undesirable effects).

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

RANEGA is not indicated for the treatment of chronic HBV infection. The safety and efficacy of RANEGA 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 package inserts for these medicines.

Patients with chronic hepatitis B or C treated with RANEGA 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.

Immune reactivation syndrome:

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of cART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii (carinii)* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Paediatric use:

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

Geriatric use:

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

Important information about some of the ingredients of RANEGA:

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

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

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 medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in lamivudine plasma levels. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine 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.

No medicine interaction studies have been conducted using RANEGA. As RANEGA contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with RANEGA. Important medicine interaction information for RANEGA 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.

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.

Renally eliminated medicines:

Tenofovir, as in RANEGA, is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of RANEGA 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 RANEGA. 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[4]	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. 1. Patients received tenofovir as tenofovir DF 300 mg once daily
2. 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 medicines and tenofovir disoproxil fumarate.

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 Parameters1 (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 contracep-tives[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.

Lamivudine:

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)

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 RANEGA.

Zidovudine has no effect on the pharmacokinetics of RANEGA.

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 patient also has renal impairment. Administration of co-trimoxazole with the lamivudine/ zidovudine combination in patients with renal impairment should be carefully assessed.

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.

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

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in RANEGA plasma levels. Unless the patient has renal impairment, no dosage adjustment of RANEGA is

necessary. RANEGA 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 RANEGA 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 section 4.5 Interaction with other medicines and other forms of interaction).

Dolutegravir:

Table 3: Medicine Interactions:

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TIVICAY or Concomitant Medicine**	**Clinical comment**
HIV-1 Antiviral Agents		
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. RANEGA should not be used with etravirine without co-administration of atazanavir + ritonavir, darunavir + ritonavir or lopinavir + ritonavir.
Non-nucleoside Reverse Transcriptase inhibitor:	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39%	Efavirenz decreased dolutegravir plasma concentrations. The

Efavirenz (EFV)	C_T ↓ 75 % EFV ↔	recommended dose of dolutegravir contained in RANEGA 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 RANEGA 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_T ↑ 180 %	Atazanavir increased dolutegravir plasma concentrations. No dose adjustment is necessary.

	ATV ↔	
Protease inhibitor: Atazanavir/ ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 33 % C_T ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment in necessary.
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 RANEGA 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 ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. 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 %	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a

	LPV ↔ RTV ↔ ETR ↔	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 Agents		
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 RANEGA is contra-indicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3 Contraindications).
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine	Dolutegravir ↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these

St. John's wort		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. RANEGA 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 %	RANEGA 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 % C_{max} ↓ 57 % C_{24} ↓ 56 %	RANEGA is recommended to be 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.
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_{T}↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir contained in RANEGA 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 RANEGA.
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 RANEGA.

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

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

In vitro, RANEGA demonstrated no direct, or weak inhibition (IC_{50} > 50 mM) 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, RANEGA 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 medicine interaction studies, dolutegravir did not have a 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 inhibited the renal organic cation transporter 2 (OTC2). Based on this observation, RANEGA may increase plasma concentrations of medicines in which excretion is dependent upon OCTZ (dofetilide, metformin).

RANEGA should not be co-administered with polyvalent cation-containing antacids. RANEGA is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5 Interaction with other medicines and other forms of interaction).

Metformin concentrations may be increased by RANEGA.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

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 RANEGA in women of childbearing potential to exclude inadvertent (unintentional) use of RANEGA 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:

RANEGA is contraindicated in pregnancy and lactation.

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 (section 4.4 Special warnings and precautions for use).

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.

Breastfeeding:

Mothers breastfeeding their infants should not use RANEGA.

HIV infected women should not breastfeed 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 newborn was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Lamivudine is excreted in human milk at similar concentrations to those found in serum and tenofovir is excreted in breast milk. Lamivudine passes into breast milk.

Mothers taking RANEGA should not breastfeed their 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.

4.7 Effects on ability to drive and use machines

RANEGA 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 RANEGA affects them.

4.8 Undesirable effects

RANEGA can have side effects.

Psychiatric disorders:

Less frequent: depression

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

Lamivudine:

Tabulated summary of adverse reactions

Tabulated summary of adverse reactions to RANEGA and its individual components	
Frequency	**Adverse reaction**
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 section 4.4 Special warnings and precautions for use)
Nervous system disorders	
Frequent	Headache, insomnia
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
Less frequent	Pancreatitis, although a causal relationship to treatment is uncertain, rise in serum amylase
Hepato-biliary disorders	
Less frequent	Transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	
Frequent	Rash, alopecia
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	Fatigue, malaise, fever

Tenofovir disoproxil fumarate:

Tabulated summary of adverse reactions to RANEGA and its individual components	
Frequency	**Adverse reaction**
Immune system disorders	
Less frequent	Allergic reaction
Metabolism and nutrition disorders	
Frequency unknown	Hypophosphataemia, lactic acidosis
Respiratory, thoracic, and mediastinal disorders	
Frequency unknown	Dyspnoea
Gastrointestinal disorders	
Frequency unknown	Abdominal pain, increased amylase, pancreatitis
Hepato-biliary disorders	
Frequency unknown	Increased liver enzymes, hepatitis
Musculoskeletal and connective tissue disorders	
Frequent	Bone mineral density decreased
Less frequent	Rhabdomyolysis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy
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

Dolutegravir:

Tabulated summary of adverse reactions to RANEGA and its individual components	
Frequency	**Adverse reaction**
Immune system disorders	
Less frequent	Hypersensitivity, immune reconstitution syndrome
Psychiatric disorders	
Frequent	Insomnia
Nervous system disorders	
Frequent	Headache, dizziness, abnormal dreams
Gastrointestinal disorders	
Frequent	Nausea, vomiting upper abdominal pain, diarrhoea, flatulence
Less frequent	Abdominal pain, abdominal discomfort
Hepato-biliary disorders	
Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	
Frequent	Rash, pruritus
General disorders and administration site conditions	
Frequent	Fatigue

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antimicrobial (Chemotherapeutic) Agents. Antiviral agents.

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 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: The effect of dolutegravir on serum creatinine clearance (CLcr), 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 (CLcr) 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 Pharmacokinetic properties

Lamivudine:

Pharmacokinetics in adults:

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.

From intravenous studies, the mean volume of distribution is 1,3 l/kg and 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.

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, 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.

Limited data shows lamivudine penetrates somewhat 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.

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 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 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. 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 section 4.2 Posology and method of administration). 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:

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy subjects, between-subject CVb % for AUC and C_{max} ranged from ~20 to 40 % and C_T from 30 to 65 % across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw %) is lower than between-subject variability.

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. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects, approximately 0,4 to 0,5 % in subjects with moderate hepatic impairment, and 0,8 to 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients. 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 5.1 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:

Adolescents:

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to < 18 years of age) showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 mg once daily.

Table 1: Adolescent pharmacokinetic parameters

Age/weight	Dolutegravir Dose	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV %)		
		$AUC_{(0-24)}$ µg.hr/ml	C_{max} µg/ml	C_{24} µg/ml
12 to < 18 years ≥ 40 kg [a]	50 mg once daily [a]	46 (43)	3,49 (38)	0,90 (59)

[a] one subject weighing 37 kg received 35 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.

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

Croscarmellose sodium;

lactose monohydrate;

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: Aqua-II White (A22D10542): polyvinyl alcohol; titanium dioxide, polyethylene glycol, talc}.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC.

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

RANEGA will be packed in a round, blue, opaque High-Density Polyethylene (HDPE) bottle, round wide mouth, blue with blue opaque polypropylene (PP) screw closure and with wad containing aluminium induction sealing liner. Packed in an outer carton.

Pack sizes of 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 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street,

Isando,

Kempton Park, 1600

Republic of South Africa

8 REGISTRATION NUMBER(S)

52/20.2.8/0200.199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 August 2018

Date of Renewal of authorisation: 25 September 2024

10 DATE OF REVISION OF TEXT

21 November 2024