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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RARUDINE, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RARUDINE film coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir, 300 mg lamivudine and tenofovir disoproxil fumarate 300 mg.

RARUDINE contains sugar - lactose monohydrate 140 mg and mannitol 157 mg per tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White coloured, biconvex film coated modified capsule shaped bevelled edge film coated tablets debossed with ‘L160’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RARUDINE is a triple combination therapy indicated for the treatment of human immunodeficiency virus (HIV) infection in adults aged 18 years and older.

4.2 Posology and method of administration

Posology

RARUDINE should be prescribed by a health care provider experienced in the management of HIV infection.

Adults:

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

Special populations

Renal impairment:

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

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

For treatment-naïve and treatment experienced patients the recommended dose of RARUDINE is one tablet once daily.

RARUDINE is contraindicated in patients with renal impairment with creatinine clearance less than 80 mL/min (see section 4.3).

Hepatic impairment

RARUDINE is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Concomitant use with rifampicin

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given in patients taking RARUDINE (see section 4.5).

Paediatric population

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

Method of administration

Oral use.

It is recommended that RARUDINE be swallowed whole with water.

RARUDINE can usually be taken with food or between meals.

4.3 Contraindications

- Hypersensitivity to dolutegravir, lamivudine, tenofovir disoproxil fumarate or to any of the ingredients of RARUDINE
- Impairment of renal function < 80 mL/min
- Pregnancy and lactation (see section 4.6)
- Women of child-bearing age unless they are using highly effective contraception
- Co-administration 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

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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.

RARUDINE is not indicated for the treatment of chronic hepatitis B virus (HBV) infection. The safety and efficacy of RARUDINE has not been established in patients 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 RARUDINE and are co-infected with HBV and HIV.

If appropriate, initiation of anti-hepatitis B therapy may be warranted.

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

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

General:

HBV antibody testing should be offered to all individuals before initiating lamivudine and tenofovir disoproxil-containing therapies (see below Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infections).

Metabolic abnormalities

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

Lipodystrophy:

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy. 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.

Consideration should be given to the measurement of serum lipids and blood glucose. 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 reactions present 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 antiretroviral therapy (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.

Raised liver enzymes, consistent with IRIS, occurred in some patients who also had hepatitis B or C infection at the start of dolutegravir therapy. Monitoring of liver function is recommended in patients with hepatitis B or C infection. Particular care should be taken in initiating or maintaining effective hepatitis B therapy when starting dolutegravir-based therapy in patients with hepatitis B.

Osteonecrosis:

Osteonecrosis has been reported particularly in patients with advanced HIV disease or following long-term combination cART. Their aetiology can be multifactorial and include corticosteroid use, excessive alcohol consumption, severe immunosuppression, and being overweight. Patients should be advised to speak to their health care provider if they have joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving RARUDINE or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by health care providers experienced in the treatment of HIV associated diseases.

Transmission of HIV:

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

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 RARUDINE. 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/ litre) and respond as follows:

- Lactate 2-5 mmol/litre: monitor regularly and be alert for clinical signs.
- Lactate 5-10 mmol/litre without symptoms: monitor closely.
- Lactate 5-10 mmol/litre with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, hyperthyroidism, lymphoma).
- Lactate > 10 mmol/litre: 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 RARUDINE alone or in combination, in the treatment of HIV infection. Most cases were women. Caution should be exercised when administering RARUDINE to patients with known risk factors for liver disease.

Treatment with RARUDINE should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatoxicity. Caution should be exercised when administering nucleoside analogues as contained in RARUDINE 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.

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

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues can cause a variable degree of mitochondrial damage *in vitro* and *in vivo*. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse events are haematological (anaemia, neutropenia) and metabolic (hyperlactataemia, hyperlipidaemia). These events are often transitory. Some late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently 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. These findings do not affect national recommendations on antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Pancreatitis:

Pancreatitis has been observed in some patients receiving lamivudine, as in RARUDINE. 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. Treatment with RARUDINE should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

Patients with renal impairment:

The terminal half-life of RARUDINE is increased in patients with moderate to severe renal impairment due to decreased clearance (see section 4.3).

Renal impairment:

RARUDINE is a combination medicine and the dose of the individual components cannot be altered.

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

RARUDINE is not recommended for patients with creatinine clearance < 80 mL/min, or patients requiring haemodialysis. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice (see section 4.8). Careful monitoring of renal function (serum creatinine and serum phosphate) is therefore recommended before therapy commences.

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:

Renal function (creatinine clearance and serum phosphate) assessment in all patients, prior to initiating therapy with tenofovir disoproxil fumarate, with monitoring every four weeks during the first year of treatment and every three months thereafter, is recommended.

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:

RARUDINE should be avoided with concurrent or recent use of a nephrotoxic medicine (e.g. high-dose or multiple non-steroidal anti-inflammatory medicines, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2). If concomitant use of RARUDINE and nephrotoxic medicine is unavoidable, 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 phosphorous (see section 4.5).

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 (see section 4.5).

K65R mutation:

RARUDINE 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 RARUDINE. Decreases in bone mineral density of the hip is significantly greater. Clinically relevant bone fractures have been 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.

RARUDINE 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 abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). 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 for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients.

Liver disease:

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

The safety and efficacy of RARUDINE 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

Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infections:

RARUDINE is not indicated for the treatment of chronic HBV infection. The safety and efficacy of RARUDINE 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 combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. Healthcare providers 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, the relevant product information for these medicines must be referred to.

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 exacerbations 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 reported with integrase inhibitors, including dolutegravir as in RARUDINE, and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect medicine should be discontinued immediately if hypersensitivity reactions develop (including severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, and angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored and appropriate therapy initiated. Delay in stopping treatment with RARUDINE or other suspect medicine after the onset of hypersensitivity may result in a life-threatening reaction.

HIV-1 resistant to integrase inhibitors

The decision to use dolutegravir in the presence of HIV-1 resistance to integrase inhibitors should take into account that it is considerably less active against viral strains with Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I. Dolutegravir's contribution to efficacy is uncertain when it is used to treat HIV-1 with this type of resistance to integrase inhibitors.

Co-administration of other medicines:

Caution should be given to co-administering medicines (prescription and non-prescription) that may change the exposure of dolutegravir or medicines that may have their exposure changed by dolutegravir (see sections 4.3 and 4.5).

The co-administration of dolutegravir 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).

The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin (see section 4.5).

Dolutegravir should not be co-administered with polyvalent cation-containing antacids. Dolutegravir is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).

Metformin concentrations may be increased by dolutegravir. Metformin is contra-indicated in patients taking dolutegravir (see section 4.3).

Paediatric use:

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

Elderly patients:

Elderly patients are more likely to have decreased renal function; therefore, caution should be exercised when treating elderly patients with tenofovir disoproxil as in RARUDINE. Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Excipients:

RARUDINE contains lactose and mannitol. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 (as in RARUDINE). Zidovudine has no effect on the pharmacokinetics of lamivudine. Lamivudine may inhibit the intracellular phosphorylation of

zalcitabine when the two medicines are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

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 RARUDINE. As RARUDINE contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with RARUDINE. Important medicine interaction information for RARUDINE is summarised in Tables 1, 2 and 3. The medicine interactions described are based on studies conducted with tenofovir disoproxil fumarate or lamivudine as individual medicines or are potential medicine interactions. While the tables include potentially significant interactions, they are not all inclusive. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450-mediated interactions involving tenofovir with other medicines is low.

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, as contained in RARUDINE in patients with renal impairment should be carefully assessed.

Renally eliminated medicines:

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

Co-administration of RARUDINE 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 RARUDINE.

Interactions relevant to tenofovir disoproxil fumarate:

Tenofovir has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, 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.

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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 mg once	8	⇔	⇔	NC
Adefovir dipivoxil	10 mg once	22	⇔	⇔	⇔
Atazanavir	400 mg once daily x 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Didanosine (enteric-coated)	400 mg once	25	⇔	⇔	⇔
Didanosine (buffered)	250 mg or 400 mg once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 mg once daily x14 days	29	⇔	⇔	⇔
Emtricitabine	200 mg once daily x 7 days	17	⇔	⇔	⇔

Indinavir	800 mg three times daily x 7 days	13	↑14 (↑3 to ↑33)	⇔	⇔
Lamivudine	150 mg twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 mg twice daily x 14 days	24	⇔	↑ 32 (↑25 to ↑38)	↑ 51 (↑37 to ↑66)
1. Patients received as tenofovir disoproxil fumarate 300 mg once daily. 2. Increase =↑; Decrease =↓; No Effect =⇔; NC =Not calculated					

Following multiple dosing to HIV-negative patients 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 medicine in the presence of tenofovir:

Co-administered medicine	**Dose of co-administered medicine (mg)**	N	**% change of co-administered medicines Pharmacokinetic[1] parameters (90 % CI)**

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			C_{max}	AUC	C_{min}
Abacavir	300 mg once	8	↑122 (↑1 to ↑26)	⇔	NA
Adefovir dipivoxil	10 g once	22	⇔	⇔	NA
Efavirenz	600 mg once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 mg once daily x 7days	17	⇔	⇔	⇔
Indinavir	800 mg three times daily x 7days	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 mg once daily x 14 Days[3]	13	⇔	⇔	⇔
Oral Contraceptives[4]	Ethinyl estradiol/	20	⇔	⇔	⇔

	Norgestimate (OrthoTricyclen®) Once daily x 7days				
Ribavirin	600 mg once daily	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 = ⇔ ; NC =Not calculated

2. R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 300 mg.

3. Individual patients 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 where equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 300 mg.
5. RSA Innovator Volutrip Prescribing Information
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.

Interactions relevant to lamivudine:

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Zidovudine plasma levels are not significantly altered when co-administered with RARUDINE.

Zidovudine has no effect on the pharmacokinetics of RARUDINE.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no

dosage adjustments are necessary.

Table 3: Medicine interactions study reports with lamivudine:

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Concomitant medicine class: Medicine name	**Effect on concentration of lamivudine or concomitant medicine**	**Clinical comment**
Trimethoprim/ sulfamethoxazole (cotrimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑ 40 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of cotrimoxazole used for the treatment

		of *Pneumocystis jirovecl (P. carinii)* pneumonia and toxoplasmosis has not been studied. RARUDINE should not be used for patients with CLcr of <50 mL/min (see section 4.3)
Zalcitabine		Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. RARUDINE is therefore not recommended to be used in combination with zalcitabine.
Zidovudine	AUC ↔	Co-administration of zidovudine results in a 13 % increase in zidovudine exposure

		and 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore, no dosage adjustments are necessary.

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

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

Interactions relevant to dolutegravir sodium:

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

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

Effect of dolutegravir as in RARUDINE on the pharmacokinetics of other medicines:

In vitro, dolutegravir as in RARUDINE, demonstrated no direct, or weak inhibition (IC50 > 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, OATP1B1, OATP1B3, OCT1 or MRP2.

In vitro, dolutegravir as in RARUDINE did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, dolutegravir 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 medicines (such as sildenafil, tadalafil, vardenafil), aciclovir, valaciclovir, sitagliptin, adefovir). In medicines interaction study reports, 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 as in RARUDINE inhibited the renal organic cation transporter 2 (OCT2). Based on this report, dolutegravir may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see Table 4).

Effect of other medicines on the pharmacokinetics of dolutegravir:

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

Co-administration of RARUDINE and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 4).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir, as in RARUDINE, significantly and require

dolutegravir dose adjustment to 50 mg twice daily. Etravirine also reduced plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore, no RARUDINE dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of RARUDINE. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 4: Medicine Interactions - HIV-1 Antiviral Medicines).

A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no RARUDINE dose adjustment is required when co-administered with these medicines.

Table 4: Medicine interactions

Concomitant medicine class: Medicine name	**Effect on concentration of dolutegravir or**	**Clinical comment**

	concomitant medicine	
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 %; C_{max} ↓ 52 %; C_T ↓ 88 % Etravirine ↔	Etravirine decreased dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir 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 % Efavirenz ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir 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 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 % ATV↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.

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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 is 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 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)	Dolutegravir ↔ 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 %	Darunavir/ritonavir did not change dolutegravir plasma concentrations to a clinically relevant extent.

	DRV↔ RTV↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDF)	Dolutegravir↔ TFV↔	Tenofovir did not change dolutegravir plasma concentration to 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 dolutegravir is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see Section 4.3).
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 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir

	C_{24}↓ 74 %	plasma concentration. Dolutegravir 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 %	Dolutegravir 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 %	Dolutegravir 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. Metformin is contraindicated in patients

		taking dolutegravir (see section 4.3).
Rifampicin	Dolutegravir↓ AUC↓ 54 % C_{max}↓ 43 % C_T↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir 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}↓ 2 % C_T↓ 7 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.

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 dolutegravir.
Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration; C_T = concentration at the end of dosing interval.		

RARUDINE should not be co-administered with polyvalent cation-containing antacids. It is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).

RARUDINE may increase metformin concentrations therefore, metformin is contraindicated in patients taking RARUDINE (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

RARUDINE should not be prescribed in women who plan to become pregnant. Women of childbearing age should not use RARUDINE unless they are using highly effective contraception.

Treatment with RARUDINE should not be initiated without a medically supervised negative pregnancy test. This test should be repeated at frequent intervals during treatment with RARUDINE and

especially in the event that pregnancy is suspected.

Pregnancy

RARUDINE is contraindicated in pregnancy. Neural tube defects have been noted in an observational study in humans, where DTG-bases regimens were used at the time of conception and early pregnancy (see section 4.3).

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

Lactation

RARUDINE is contraindicated in lactation.

Mothers breastfeeding their infants should not use RARUDINE. Lamivudine is excreted in human milk at similar concentrations to those found in serum; tenofovir is excreted in breast milk and it is not known whether dolutegravir is excreted in human milk.

Fertility

There are no data on dolutegravir's effects on human male or female fertility, although animal studies indicate no harmful effects of dolutegravir, lamivudine and tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines:

RARUDINE may affect the ability to drive and use machines as RARUDINE can cause dizziness. Patients should ensure that they do not engage in driving or using machines until they know how RARUDINE affects them.

4.8 Undesirable effects

Summary of the safety profile

Studies revealed the most severe adverse reactions linked to dolutegravir treatment are hypersensitivity reactions that include rash and severe liver effects. The most common adverse reactions of dolutegravir are nausea (13 %), diarrhoea (18 %) and headache (13 %).

Renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported rarely in patients receiving tenofovir disoproxil. Monitoring of renal function is recommended for patients receiving RARUDINE (see section 4.4).

Tabulated list of adverse effects

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Adverse effects for RARUDINE:

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Neutropenia, anaemia, thrombocytopenia, pure red cell aplasia
Immune system disorders	Less frequent	Hypersensitivity, immune reactivation syndrome
Metabolism and nutrition disorders	Frequent Less frequent Frequency unknown	Hypophosphatemia Lactic acidosis Hypokalaemia
Psychiatric disorders	Frequent Less frequent	Insomnia, abnormal dreams, depression, anxiety Suicidal ideation or suicide attempt
Nervous system disorders	Frequent Less frequent	Headache, dizziness Peripheral neuropathy paraesthesia
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough, nasal symptoms Dyspnoea

Gastrointestinal disorders	Frequent Less frequent	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort Pancreatitis, elevated serum amylases
Hepato-biliary disorders	Less frequent Frequency unknown	Hepatitis Hepatic steatosis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, hair loss
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Arthralgia, myalgia Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, osteonecrosis

Renal and urinary disorders	Less frequent Frequency unknown	Rare acute renal failure, renal failure, proximal renal tubulopathy (including Fanconi syndrome), increased serum creatinine, acute tubular necrosis Nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Fatigue, malaise, fever Asthenia Immune reconstitution syndrome
Investigations	Frequent	Raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) raised creatine kinase

Side effects for Dolutegravir:

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Less frequent	Hypersensitivity, immune reconstitution syndrome

Psychiatric disorders	Frequent	Insomnia
Nervous system disorders	Frequent	Headache, dizziness, abnormal dreams
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Nausea, diarrhoea Vomiting, flatulence, upper abdominal pain Abdominal pain, abdominal discomfort
Hepato-biliary disorders	Frequency unknown	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus

Side effects for Lamivudine:

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent Frequency unknown	Neutropenia, anaemia, thrombocytopenia Pure red cell aplasia

Metabolism and nutrition disorders	Frequent Less frequent	Hyperlactataemia Lactic acidosis, lipodystrophy
Nervous system disorders	Frequent Less frequent	Headache, insomnia Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children exposed *in utero*
Gastrointestinal disorders	Frequent Less frequent	Nausea, diarrhoea, vomiting, upper abdominal pain or cramps, stomatitis Pancreatitis, rises in serum amylase
Hepato-biliary disorders	Less frequent	Transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Arthralgia, muscle disorders

		Rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures
General disorders and administrative site conditions	Frequent	Fatigue, malaise, fever

Side effects for Tenofovir disoproxil fumarate:

System Organ Class	**Frequency**	**Side effects**
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	Frequent Less frequent	Abdominal pain, anorexia, dyspepsia, flatulence Increased amylase, pancreatitis
Hepato-biliary disorders	Less frequent	Increased liver enzymes, hepatitis

Renal and urinary disorders	Frequent	Renal insufficiency, renal failure, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic, diabetes insipidus

a. Description of selected adverse reactions

Changes in serum creatinine

Serum creatinine can increase in the first week of treatment with dolutegravir and then remain stable. A mean change from baseline of 10 µmol/litre occurred after 48 weeks of treatment. Creatinine increases were comparable between various background regimens. These changes are not considered clinically relevant since they do not reflect a change in glomerular filtration rate.

Immune reactivation syndrome

In HIV patients with severe immune deficiency at the start of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the time to onset is more variable and these events can occur many months after starting treatment (see section 4.4).

Renal impairment

As lamivudine and tenofovir disoproxil may cause renal damage, monitoring of renal function is recommended (see section 4.4). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medicines) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

Renal tubulopathy

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not likely to be causally associated with tenofovir disoproxil therapy in the absence of proximal renal tubulopathy.

Interaction with didanosine

Co-administration of tenofovir disoproxil and didanosine is not recommended as it results in a 40-60 % increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Co-infection with hepatitis B or C

When taking dolutegravir, as contained in RARUDINE, the rates of AST and ALT abnormalities may be higher in patients with hepatitis B or C co-infection. Liver enzymes elevations consistent with immune reactivation syndrome may occur in some subjects with hepatitis B or C co-infection at the start of RARUDINE therapy, particularly in those whose hepatitis B therapy was stopped. The side effect profile in patients also infected with hepatitis B or C or both are similar to that of patients without hepatitis, provided that the baseline liver function tests does not exceed 5 time the upper limit of normal.

Limited data on patients co-infected with HIV/HBV or HIV/HCV indicate that the adverse reaction profile of emtricitabine and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection.

However, as would be expected, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis may occur after discontinuation of treatment (see section 4.4).

b. Other special populations

Elderly

Caution should be exercised since elderly patients are more likely to have decreased renal function.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms:

If overdose occurs the patient must be monitored for evidence of toxicity (see sections 4.8 and 5.3), and standard supportive treatment applied as necessary.

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 overdose in humans. If overdosage occurs the patient should be monitored, and palliative supportive treatment applied are 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 RARUDINE. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As RARUDINE is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antivirals, Antivirals for treatment of HIV infections, combinations, ATC code: J05AR12

Pharmacological classification: A.20.2.8 Antiviral agents.

Mechanism of action

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 active 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

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 DNA chain termination.

Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Medicine Resistance:

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro* and a K65R mutation in reverse transcriptase have been selected *in vitro* and, in some patients, treated with tenofovir and in combination with certain antiretroviral medicines.

In treatment naïve patients treated with tenofovir + lamivudine + efavirenz, viral isolates from 17 % of 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 selected by tenofovir is also selected in some HIV-1 infected patients treated with 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 reported.

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 S135Y 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 wild type subtype B, C and A/G viruses in the presence of dolutegravir selected for R263K, G118R and S153T.

Anti-HIV activity Against Resistant Strains:

Reverse Transcriptase Inhibitor and Protease Inhibitor-Resistant strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wild-type strain.

Integrase Inhibitor-Resistant HIV-1 Strains:

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

Integrase Inhibitor-Resistant HIV-2 Strains*:*

Site directed mutant HIV-2 viruses were constructed based on 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 increase 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:

Absorption:

Lamivudine is well absorbed from the gastrointestinal tract and the bioavailability of oral lamivudine in adults is normally between 80 % and 85 %. 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 reported.

Distribution and elimination:

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.

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

Linearity:

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

Interactions:

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary. The likelihood of adverse interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

APPROVED PROFESSIONAL INFORMATION

Dolutegravir

Dolutegravir pharmacokinetics are reported as similar between healthy and HIV-infected patients. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy patients, inter-patient CVb % for AUC and C_{max} ranged from ~20 to 40 % and CT from 30 to 65 % across studies. The interpatient PK variability of dolutegravir was higher in HIV-infected patients than healthy patients. Intra-patient variability (CVw %) is lower than interpatient 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, an 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 proteins was independent of concentration.

Total blood and plasma medicine-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 patients, approximately 0,4 to 0,5 % in patients with moderate hepatic impairment and 0,8 to 1,0 % in patients with severe renal impairment and 0,5 % in HIV-1 infected patients. Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve patients on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC_{50}); CSF: plasma concentration ratio of dolutegravir ranged from 0,11 to 0,66 %.

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).

Biotransformation:

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 either 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.

Tenofovir disoproxil fumarate:

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir.

Absorption:

The oral bioavailability of tenofovir from tenofovir disoproxil fumarate 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 dose range of 75 to 600 mg and are not affected by repeated dosing.

Administration of tenofovir following a high-fat meal (~ 700 to 1000 kcal containing 40 to 50 % fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40 % and an increase in C_{max} of approximately 14 %. However, administration of tenofovir with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 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 proteins 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.

Biotransformation:

In vitro studies reported that neither tenofovir disoproxil nor tenofovir are substrates of 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.

Elimination:

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.

Pharmacokinetics in special patient groups

Tenofovir

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). Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a four-hour hemodialysis session removed approximately 10 % of the administered tenofovir dose.

Dolutegravir

Special 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 5: 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)

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 patients with severe renal impairment (CLcr < 30 mL/min). No clinically important pharmacokinetic differences between patients with severe renal impairment (CLcr < 30 mL/min) and matching healthy patients were observed, AUC, C_{max} and C24 of dolutegravir were decreased by 40 %, 23 % and 43 % respectively, compared with those in matched healthy patients. 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 patients 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 patients, patients with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32 % lower clearance of dolutegravir and 46 % higher AUC compared with patients 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 patients with hepatitis B coinfection

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.

Lamivudine
Paediatric population:

The absolute bioavailability of lamivudine (approximately 55 - 65 %) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age approaching adult values around 12 years of age. Recent findings indicate that exposure in children 2 to < 6 years of age may be reduced by about 30 % compared with other age groups. At present, the available data do not suggest that lamivudine is less efficacious in this group. There are limited pharmacokinetic data for patients < 3 months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely due to immature renal function and variable absorption.

Pharmacokinetics in pregnancy:

Lamivudine pharmacokinetics in late-pregnancy were similar to nonpregnant adults. Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia. Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenic assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 30-40 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests it is concluded that lamivudine should not represent

a genotoxic hazard to patients undergoing treatment. There is as yet no information on the tumorigenic risk in animals, and therefore any potential risk to man must be balanced against the expected benefits of treatment.

5.3 Preclinical safety data

Dolutegravir:

Dolutegravir was not mutagenic or clastogenic in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long-term studies in the mouse and rat.

Dolutegravir did not affect male or female fertility in rats at doses up to 24 times the 50 mg twice daily human clinical exposure based on AUC.

Oral administration of dolutegravir to pregnant rats at doses up to 27 times the 50 mg twice daily human clinical exposure based on AUC from days 6 to 17 of gestation did not cause maternal toxicity, developmental toxicity or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, reduced urine or faeces, suppressed bodyweight gain) was observed at 1000 mg/kg.

In a juvenile toxicity study in rats, there were two pre-weanling deaths at dolutegravir dose of 75 mg/kg daily. Over the pre-weaning period, mean bodyweight gain was decreased and

the decrease persisted throughout the study for females during the post-weaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was about 17 to 20-fold higher than in humans at the recommended paediatric exposure. No new target organs were identified in juveniles compared to adults. In the rat prenatal and postnatal development study, bodyweight decreased in the developing offspring during lactation at a maternally toxic dose (about 27 times human exposure at the maximum recommended dose).

The primary effect of high doses of dolutegravir and prolonged daily treatment (up to 26 weeks in rats and up to 38 weeks in monkeys) was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures about 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal intolerance is considered to be due to local effects of the active substance, comparison based on bodyweight or on body surface area is appropriate for this toxicity. Gastrointestinal intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50-kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

Tenofovir:

Preclinical studies in rats, dogs and monkeys revealed target-organ effects on gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats

and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities.

Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or foetal parameter. There were no gross foetal alterations of soft or skeletal tissues. Tenofovir disoproxil reduced the viability index and weight of pups in peri-post-natal toxicity studies.

Genotoxicity studies have shown that tenofovir disoproxil was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of s9 metabolic activation. Tenofovir disoproxil was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6,2- to 6,8-fold increase) and once without S9 mix. Tenofovir disoproxil was also weakly positive in an *in vivo/in vitro* unscheduled DNA synthesis test in primary rat hepatocytes.

Tenofovir disoproxil did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentration of tenofovir disoproxil in the gastrointestinal tract at a dose of 600 mg/kg/day. While the

mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

Lamivudine:

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity.

Lamivudine was not mutagenic in bacterial tests but showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vitro* at doses that gave plasma concentrations around 40–50 times higher than the expected clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed *in vivo*, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicone dioxide

Croscarmellose sodium

Hypromellose

Lactose monohydrate

Magnesium stearate (vegetable grade)

Mannitol

Microcrystalline cellulose (Avicel PH101)

Povidone

Sodium starch glycolate

Talc

Tablet coating: Opadry II White:

Macrogol

Polivinyl alcohol

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.

Discard 90 days after first opening.

6.5 Nature and contents of container

Round opaque white HDPE bottle with 38 mm child resistant closure of polypropylene with HS 12335 printed liner with two molecular sieve sachet of 5g containing 30 tablets.

Round opaque white HDPE bottle with 38 mm child resistant closure of polypropylene with HS 12335 printed liner with two molecular sieve sachets of 5g containing 60 tablets.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

This medicine does not require any special storage conditions.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER

A54/20.2.8/0343

9. DATE OF FIRST AUTHORISATION

28 March 2023

10. DATE OF REVISION OF THE TEXT