SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE TELATRI

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).

TELATRI IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. SAFETY AND EFFICACY OF TELATRI HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED THE COMBINATION TABLET. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE TELATRI AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

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

Contains sugar: Mannitol 144,5 mg per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

White to off-white film coated, caplet shaped tablets plain on both side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Adults

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

Paediatrics: TELATRI 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 **TELATRI**, was administered to patients with moderate to severe renal impairment (see section 4.3).

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

TELATRI is not suitable for use in patients with renal impairment with creatinine clearance less than 80 ml/ min.

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

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

4.3 Contraindications

- **TELATRI** tablets are contra-indicated in patients with known hypersensitivity to lamivudine, tenofovir or dolutegravir or to any of the components of the tablets.
- Impairment of renal function.
- Concomitant use with adefovir dipivoxil.
- Co-administration with dofetilide and pilsicainide.
- Co-administration with didanosine.
- Co-administration with metformin.
- 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 **TELATRI** have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination as in **TELATRI** for the treatment of HIV have not been established in clinical studies.

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

Metabolic abnormalities

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

Lipodystrophy

Combination antiretroviral therapy, including **TELATRI,** 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.

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 **TELATRI.** 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 **TELATRI** 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 **TELATRI,** 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 **TELATRI.** 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 responds 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 **TELATRI** alone or in combination, in the treatment of HIV infection. Most cases were women.

Caution should be exercised when administering **TELATRI** to patients with known risk factor for liver disease.

Treatment with **TELATRI** 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 **TELATRI** 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 **TELATRI** on clinical progression of HIV-1.

Mitochondrial dysfunction:

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

Patients with renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of **TELATRI** is increased due to the decreased clearance

(see section 4.3).

Liver disease:

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

The safety and efficacy of **TELATRI** 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:

TELATRI is a combination product and the dose of the individual components cannot be altered. Tenofovir and lamivudine are principally eliminated by the kidney. **TELATRI** is not recommended for patients with creatinine clearance <80 ml/min or patients who require haemodialysis. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) has been reported with the use of tenofovir disoproxil fumarate in clinical practice. Careful monitoring of renal function (serum creatinine and serum phosphate) is therefore recommended before taking **TELATRI.**

Renal function:

Since **TELATRI** is primarily eliminated by the kidneys, co-administration of **TELATRI** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of **TELATRI** and/or increase the concentrations of other renally eliminated medicines. Some examples include, but 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 patient 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 MPR 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.

TELATRI 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:

TELATRI 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 **TELATRI.** Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected then appropriate consultation should be obtained. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia.

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

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained. Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

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

TELATRI is not indicated for the treatment of chronic HBV infection. The safety and efficacy of **TELATRI** 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 insert for these medicines.

Patients with chronic hepatitis B or C treated with **TELATRI** 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).

Exacerbation 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 decompensation liver disease.

Immune Reconstitution Inflammatory 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. 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 (carinii)*–pneumonia, 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 may occur many months after initiation of the treatment.

Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Hypersensitivity reactions:

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

Paediatric use:

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

Use in elderly:

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

TELATRI contains mannitol and may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

The likelihood of interactions is low due to the limited metabolism and plasma protein binding and almost complete renal clearance. Zidovudine plasma levels are not significantly altered when co-administered with lamivudine. Zidovudine has no effect on the pharmacokinetics of lamivudine. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine. 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 **TELATRI.** As **TELATRI** contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with **TELATRI.** Important medicine interaction information for **TELATRI** is summarised in Tables 3, 4 and 5. The medicine interactions described are based on studies conducted with tenofovir disoproxil fumarate or lamivudine as individual medicines, or are potential medicines 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/zidovudine combination in patients with renal impairment should be carefully assessed.

Renally eliminated medicines:

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

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 3 and 4 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 increase 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 fasting conditions.

Table 2:

Medicine Interactions: Changes in pharmacokinetic parameters for tenofovir[1] in the presence of co-administered medicines:

Co-administered medicine	**Dose of Co-administered Medicine (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[2] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↔	↔	NC
Adefovir dipivoxil	10 once	22	↔	↔	↔
Atazanavir	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric coated)	400 once	25	↔	↔	↔

Didanosine (buffered)	250 or 400 once daily x 7 days	14	↔	↔	↔
Efavirenz	600 once daily x 14 days	29	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓3 to ↑ 33)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↔	↔	↔
Lopinavir/Ritonavir	400/100 twice daily x 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)

1. Patients received tenofovir DF 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 medicines interactions between these medicines and tenofovir disoproxil fumarate.

Table 3:

Medicine Interactions: Changes in pharmacokinetic parameters for co-administered medicines in the presence of tenofovir

Co-administered medicine	**Dose of Co-administered Medicine (mg)**	**N**	**% Change of Co-Administered Medicine Pharmacokinetic Parameters[1] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑122 (↑1 to ↑26)	↔	N/A
Adefovir dipivoxil	10 once	22	↔	↔	N/A
Efavirenz	600 mg once daily x 14 days	30	↔	↔	↔
Emtricitabine	200 mg once daily x 7 days	17	↔	↔	↔
Indinavir	800 mg three times daily x 7 days	12	↑14 (↓3 to ↑33)	↔	↔
Lamivudine	150 mg twice daily x 7 days	15	↔	↔	↔
Lopinavir/Ritonavir	400/100 mg twice daily x 14 days	21	↔	↔	↔

Methadone[2]	40-110 once daily x 14 days[3]	13	↔	↔	↔
Oral contraceptives[4]	Ethinyl ~~e~~estradiol/Norgestimate (Ortho-Tricyclen®) Once daily x 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	N/A
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 patients were maintained on their stable methadone dose. No pharmacodynamics alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
4. Ethinyl ~~e~~estradiol 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.

Tenofovir disoproxil fumarate should not be administered concomitantly with other medicines containing tenofovir disoproxil fumarate or tenofovir alafenamide.

Renally eliminated medicines

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil fumarate with *medicines* that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) may increase serum concentrations of tenofovir and/or the co-administered medicines.

Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicines. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

Tacrolimus can affect renal function; close monitoring is recommended when it is co-administered with tenofovir disoproxil fumarate.

Other interactions: Interactions between tenofovir disoproxil fumarate and other medicines are listed in **Table 4 below.**

Table 4:

Interactions between tenofovir disproxil fumarate and other medicines

Medicines by therapeutic area (dose in mg)	Effect on medicine levels mean percent change in AUC, C_{max}, C_{min}	Recommendations on co-administration with 245 mg tenofivir disoproxil (as fumarate)
Anti-infectives		
Anitretrovirals		
Protease Inhibitors (PIs)		
Darunavir/Ritonavir (300 mg/100 mg twice daily / 300 mg OD)	Darunavir: No significant effect on darunavir/ritonavir Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored.
Hepatitis C virus medicines		

Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Atazanavir/Ritonavir (300 mg/100 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/300 mg once daily)[1]	Ledipasvir: AUC: ↑ 96% C_{max}: ↑ 68% C_{min}: ↑ 118% Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 63% Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 45% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 47% C_{min}: ↑ 47%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been reported. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available**.**

Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Darunavir/Ritonavir (800 mg/100 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg / 300 mg once daily)[1]	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↓ 27% C_{max}: ↓ 37% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 48% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50% C_{max}: ↑ 64% C_{min}: ↑ 59%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been reported. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available**.**

Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Efavirenz/Emtricitabine/ Tenofovir disoproxil fumarate (600 mg/200 mg/300 mg once daily)	Ledipasvir: AUC: ↓ 34% C_{max}: ↓ 34% C_{min}: ↓ 34% Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 98% C_{max}: ↑ 79% C_{min}: ↑ 163%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored**.**

Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil fumarate (200 mg/25 mg/300 mg once daily)	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↔ C_{min}: ↑ 91%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored**.**

Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Dolutegravir (50 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/300 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2] AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Dolutegravir AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 65% C_{max}: ↑ 61% C_{min}: ↑ 115%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored**.**

Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Atazanavir/Ritonavir (300 mg mg once daily./100 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/300 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% Velpatasvir: AUC: ↑ 142% C_{max}: ↑ 55% C_{min}: ↑ 301% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 39% Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 29% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 55% C_{min}: ↑ 39%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring.

Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Darunavir/Ritonavir (800 mg q.d./100 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/300 mg once daily)	Sofosbuvir: AUC: ↓28% C_{max}: ↓ 38% GS-3310072[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 24% C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% C_{max}: ↑ 55% C_{min}: ↑ 52%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, sofosbuvir/velpatasvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring.

Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Lopinavir/Ritonavir (800 mg/200 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/300 mg once daily)	Sofosbuvir: AUC: ↓ 29% C_{max}: ↓ 41% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 30% C_{min}: ↑ 63% Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 42% C_{min}: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring.

Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Raltegravir (400 mg twice daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/300 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Raltegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 21% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↑ 46% C_{min}: ↑ 70%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored.

Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Efavirenz/Emtricitabine/ Tenofovir disoproxil fumarate (600 mg/200 mg/300 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 38% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↓ 53% C_{max}: ↓ 47% C_{min}: ↓ 57% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 81% C_{max}: ↑ 77% C_{min}: ↑ 121%	Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma concentrations of velpatasvir. Co-administration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.

Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil fumarate (200 mg/25 mg/300 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↑ 44% C_{min}: ↑ 84%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored**.**

Sofosbuvir (400 mg once daily) + Efavirenz/Emtricitabine/ Tenofovir disoproxil fumarate (600 mg/200 mg/300 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19% GS-331007[2]: AUC: ↔ C_{max}: ↓ 23% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25% C_{min}: ↔	No dose adjustment is required.

[1] Data reported from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.

[2] The predominant circulating metabolite of sofosbuvir.

Other medicines

There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was reportedly co-administered with emtricitabine, lamivudine, indinavir, efavirenz, nelfinavir, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus or the hormonal contraceptive norgestimate/ethinyl ~~o~~estradiol.

Lamivudine:

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

Zidovudine plasma levels are not significantly altered when co-administered with **TELATRI**. Zidovudine has no effect on the pharmacokinetics of **TELATRI.**

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.

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

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in **TELATRI** plasma levels. Unless the patient has renal impairment, no dosage adjustment of **TELATRI** is necessary. **TELATRI** has no effect on the pharmacokinetics of co-trimoxazole. Administration of co-trimoxazole with the **TELATRI** in patients with renal impairment should be carefully assessed.

The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route is renal.
The co-administartion of **TELATRI** with etravine (ETR) is not recommended unless the patient is also receiving concomitant atrazanivir + ritonavir (ATV + RTV), lopinavir + ritonavir (DRV + RTV).

Other medicines (e.g. ranitidine, cimetidine) are eliminated only in part by active renal secretion via the organic cationic transport system and were reported not to interact with lamivudine. The nucleoside analogues (e.g. didanosine) like zidovudine, are not eliminated by this mechanism and are unlikely to

interact with lamivudine. Due to similarities, lamivudine should not be administered concomitantly with other cytidine analogues, such as emtricitabine.

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some of the reported clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended.

Lamivudine metabolism does not involve CYP3A, making interactions with medicines metabolised by this system (e.g. PIs) unlikely.

Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in a reported dose-dependent decreases of 14 %, 32 %, and 36 % in lamivudine exposure (AUC_{∞}) and 28 %, 52 %, and 55 % in the C_{max} of lamivudine in adults. When possible, avoid chronic co-administration of **TELATRI** with medicines containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

Dolutegravir:

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

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

TELATRI should not be co-administered with polyvalent cation-containing antacids. **TELATRI** is recommended to be administered 2 hours before or 6 hours after these medicines.

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

Effect of Dolutegravir on the Pharmacokinetics of other medicines:

In vitro, dolutegravir reported no direct, or weak inhibition (IC_{50} >50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2.

In vitro, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir reportedly did not have an effect on midazolam, a CYP3A4 probe. Based on reported 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 reported 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 reportedly inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14 % decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was reported in patients. Dolutegravir may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 or MATE-1 (dofetilide, metformin) (see **Table 5: Medicine Interactions – other medicines**).

In vitro, dolutegravir was reported to inhibit the renal uptake transporters, organic anion transporters (OAT1) and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been reported to be studied *in vivo*. Dolutegravir may increase plasma concentrations of medicines in which excretion is dependent upon OAT3.

Effect of other medicines on the Pharmacokinetics of dolutegravir:

Dolutegravir is reported to be eliminated mainly through metabolism by UGT1Al. Dolutegravir 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 dolutegravir and other medicines that inhibit: UGT1A11 UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (Table 5).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir 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 dolutegravir 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 dolutegravir. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 5: HIV-1 Antiviral Medicines).

A medicine interaction study with the UGTlA1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, bocepravir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dolutegravir dose adjustment is required when co-administered with these medicines.

Table 5: Medicine Interactions

Concomitant Medicine Class: Medicine Name	Effect on Concentration of dolutegravir or Concomitant Medicine	Clinical Comment
HIV-1 Antiviral medicines		
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. 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 % EFV ↔	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.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12 % C_{max} ↑ 13 % C_T ↑ 22 % Rilpivirine ↔	No dose adjustment is necessary.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 50 % C_T ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
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 %	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

	TPV ↔ RTV ↔	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-naive 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 ↔	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 % LPV ↔ RTV ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

	ETR ↔	
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 Antiviral medicines		
Telaprevir	Dolutegravir ↑ AUC ↑ 25 % C_{max} ↑ 19 % C_T ↑ 37 % Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)	No dose adjustment is necessary
Boceprevir	Dolutegravir ↔ AUC ↑ 7 % C_{max} ↑ 5 % C_T ↑ 8 % Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33 % C_{max} ↑ 29 % C_T ↑ 45 % Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. 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 contra-indicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin ~~Phenobarbital~~ 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.
Azole anti-fungal medicines Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
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 cations decreased dolutegravir 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 % C24 ↓ 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.
Multivitamin	Dolutegravir ↓ AUC ↓ 33 % C_{max} ↓ 35 % C_{24} ↓ 32 % (Complex binding to polyvalent ions)	Multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Corticosteroids Prednisone	Dolutegravir ↔ AUC ↑ 11 % C_{max} ↑ 6 % C_T ↑ 17 %	No dose adjustment is necessary.
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking dolutegravir (see section 4.3).
Antimycobacterials Rifabutin	Dolutegravir ↔ AUC ↓ 5 % C_{max} ↑ 16 % C_T ↓ 30 % (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Antimycobacterials 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 Norelgestromin (NGMN)	Effect of Dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % Cт ↑ 2 % Effect of Dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % Cт ↓ 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 dolutegravir.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % Cт ↓ 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, Ct =concentration at the end of dosing interval.

Paediatric population

Interaction studies have only been reported to be performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

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

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

Pregnancy

Use of dolutegravir during pregnancy was associated with a small increase in the prevalence of neural tube defects (0,19 %) compared to non-dolutegravir regimens (0,11 %). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

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

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

Breastfeeding

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

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

Lamuvidine passes into breast milk. It is unknown whether tenofovir passes into breast milk. HIV infected women should not breastfeed their babies in order to avoid transmission of HIV to the baby.

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

TELATRI 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 **TELATRI** affects them.

4.8 Undesirable effects

Body System	Lamivudine	Tenofovir Disoproxil Fumarate	Dolutegravir
Blood and lymphatic systems disorders	*Less frequent:* Neutropenia; anaemia, thrombocytopenia *Frequency unknown:* pure red cell aplasia		
Immune system disorders	*Frequency unknown:* Autoimmune disorders (Graves' disease) (see section 4.4). *Less frequent:* Angioedema	*Less frequent:* Allergic reaction, angioedema	*Less Frequent:* Hypersensitivity; Immune Reconstitution syndrome

Metabolism and nutrition disorders	*Frequent:* Hyperlactataemia *Less frequent*: Lactic acidosis; lipodystrophy (redistribution/accumulation of body fat) (see section 4.4). *Frequency unknown*: weight increase	*Frequent*: Hypophosphataemia, lipodystrophy, weight loss *Less frequent:* Lactic Acidosis, hypokalaemia *Frequency unknown:* weight increase	
Psychiatric disorders			*Frequent:* Insomnia, Depression, Anxiety *Less Frequent:* Suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)

Nervous system disorders	*Frequent:* Headache; insomnia *Less frequent:* Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children exposed *in utero*.	*Frequent*: Dizziness, headache, depression, insomnia, peripheral neuropathy, anxiety	*Frequent:* Headache, Dizziness, Abnormal dreams
Respiratory, Thoracic and mediastinal disorders	*Frequent:* Cough, nasal symptoms	*Frequent:* Pneumonia *Frequency unknown:* Dyspnoea,	
Gastrointestinal disorders	*Frequent:* Nausea, vomiting; upper abdominal pain or cramps; diarrhoea *Less frequent:* Pancreatitis; elevations in serum amylase	*Frequent:* Abdominal pain; anorexia; dyspepsia; flatulence; diarrhoea; vomiting, nausea *Less frequent:* Increased amylase; pancreatitis	*Frequent:* Nausea; Diarrhoea *Less Frequent:* Vomiting; flatulence; upper abdominal pain *Frequency not known:* Abdominal pain; abdominal discomfort

Hepatobiliary disorders	*Less frequent:* Transient rises in liver enzymes (AST, ALT); hepatitis	*Less frequent:* Increased liver enzymes; hepatitis, hepatic steatosis	*Frequency not known:* Hepatitis
Skin and subcutaneous tissue disorders	*Frequent:* Rash; alopecia	*Frequent:* Rash (pruritis, maculopapular rash, urticarial, vesiculobullous rash, pustular rash), sweating	*Frequent:* Rash; pruritus
Musculoskeletal and connective tissue disorders	*Frequent:* arthralgia, muscle disorders *Less frequent:* rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures *Frequency unknown:* Osteonecrosis (see section 4.4).	*Frequent:* Arthralgia, myalgia *Less frequent:* Rhabdomyolysis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy *Frequency unknown:* Osteonecrosis (see section 4.4)	*Less Frequent:* Arthralgia; Myalgia

Renal and urinary disorders		*Frequent:* Renal insufficiency; renal failure; proximal tubulopathy; proteinuria; increases creatinine; acute tubular necrosis; nephrogenic diabetes insipidus. *Less frequent:* acute renal failure, nephritis (including acute interstitial nephritis) *Frequency unknown:* Fanconi syndrome	
General disorders and administration site conditions	*Frequent:* fatigue, malaise, fever	*Frequent:* Asthenia, pain, fever, back pain, chest pain	*Frequent:* Fatigue

Investigations	*Frequency unknown*: levels of blood lipids and glucose may increase	*Frequent:* Grade 3 and 4 laboratory abnormalities in total cholesterol, triglyceride, creatine kinase, haematuria, neutrophil, urine glucose and serum glucose. *Frequency unknown:* Levels of blood lipids and glucose may increase.	*Frequent:* Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations; Creatine phosphokinase (CPK) elevations *Frequency unknown*: increase in serum creatinine and total bilirubin (without clinical jaundice)

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com or Tel: +27(0) 12 643 2000

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 **TELATRI**. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As dolutegravir 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: Category A, 20.2.8 Antiviral Agents

ATC Code: JO5AR02

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

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, 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 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 the 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 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.

5.2 Pharmacokinetic properties

A Fixed Dose Combination of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (50mg/300mg/300 mg) is bioequivalent to Tivicay® (dolutegravir) Tablets 50 mg, Epivir® Tablets (lamivudine) 300 mg and Viread® (tenofovir disoproxil fumarate) Tablets 300 mg when these medicines are administered under fasting condition.

The pharmacokinetics of fixed dose combination following oral administration of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (50mg/300mg/300 mg) was investigated in 62 healthy adult subjects under fasting condition. Pharmacokinetic parameters for Dolutegravir, Lamivudine and Tenofovir

Disoproxil Fumarate Tablets (50mg/300mg/300 mg) following single oral doses in healthy subjects are presented in Table 1.

Table 1: Pharmacokinetic Parameters for Fixed Dose Combination of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (50mg/300mg/300 mg) after single dose administration

Analyte	C_{max} (ng/mL) Mean (±SD)	T_{max} (hr)# Median (Range)	AUC_{0-t} (ng•hr/mL) Mean (±SD)	$t_{1/2}$ (hr) Mean (±SD)
Dolutegravir (N = 62)	2636.58 (588.506)	2.333 (0.833-6.000)	46324.2763 (12529.26580)	15.4347 (3.07856) *
Lamivudine (N = 62)	2270.47 (656.441)	2.000 (0.833-4.000)	12182.8019 (3360.73505)	7.5067 (4.83422)
Tenofovir (N = 62)	467.896 (112.8949)	0.833 (0.500-1.667)	3064.2371 (800.70445)	18.0185 (2.975) *

Median (Range); *N = 59 for $t_{1/2}$

Lamivudine

Adults:

Lamivudine is well absorbed from the gastrointestinal tract and the reported bioavailability of oral lamivudine in adults is normally between 80 % and 85 %. Following oral administration, the reported 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 reported to be in the order of 1-1,5 µg/ml. From intravenous studies, the reported mean volume of distribution is 1,3 L/kg and reported mean terminal half-life of elimination is 5 to 7 hours. The reported 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 reported to be 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.

Lamivudine has been reported to 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.

It was reported that 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 medicine interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

A reported 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 3TC/zidovudine combination in patients with renal impairment should be carefully assessed. It was reported from limited data that lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The reported mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0,12.

Tenofovir

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

Absorption:

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The reported 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}) was reported to be achieved in 1,0 ± 0,4 hrs. Reported C_{max} and AUC values were 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.

Effects of food on Oral Absorption:

Administration of tenofovir following a high-fat meal (~700 to 1000 kcal containing 40 to 50 % fat) reportedly 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 been reported for 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 reported to be 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 reported to be 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 reported that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following single dose, oral administration of tenofovir, the reported 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 reported to be recovered in urine over 24 hours.

Tenofovir is reported to be 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:

The pharmacokinetics of tenofovir following 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. No change in tenofovir dosing is required in patients with hepatic impairment.

Renal impairment:

The pharmacokinetics of tenofovir 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

Dolutegravir pharmacokinetics are reported to be similar between healthy subjects and HIV-infected patients. The reported PK variability of dolutegravir is between low to moderate. In Phase 1 reported 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 reported to be higher in HIV-infected patients than healthy subjects. Within-subject variability (CVw %) is reported to be lower than between-subject variability.

Absorption:

Dolutegravir is reported to be 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 reported to be dependent on dose and formulation. Following oral administration of tablet formulations, dolutegravir was reported to exhibit 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 reportedly 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 $_{0-\infty}$ 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 reported to be clinically significant.
The absolute bioavailability of dolutegravir has not been reported to be established.

Distribution:
Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on reported *in vitro* data. The reported 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 reported to be 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 reportedly estimated at approximately 0,2 to 1,1 % in healthy subjects, 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 reported to be present in cerebrospinal fluid (CSF). In 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 reportedly exceeded the IC_{50}, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy.

Metabolism:

Dolutegravir is reported to be primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a reported 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 reported to be 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 reported to be 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.

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 patients 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 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 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.

The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated. A small decrease of 10-14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

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 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 the 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 co-infection.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Croscarmellose sodium
- Magnesium stearate
- Mannitol
- Microcrystalline cellulose
- Povidone
- Sodium starch glycolate

Coating material: Opadry II 85F580019 (White)

- Macrogol/PEG
- Polyvinyl alcohol-part hydrolysed
- Talc
- Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from moisture and light.

Keep in the original container until required for use.

Keep the container tightly closed.

6.5 Nature and contents of container

The film coated tablets are packed in a white opaque HDPE bottle pack of 28's, 30's, 84's and 90's with 3 g silica or 5 g silica as desiccant and a white opaque polypropylene screw cap with an induction seal liner; with or without a carton.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road,

Stormill, Ext.1, Roodepoort

Johannesburg

1724

Telephone: +27(0) 12 643 2000

8. REGISTRATION NUMBER(S)

TELATRI: 52/20.2.8/0718 **TELATRI:**

52/20.2.8/0719.718

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2018

10. DATE OF REVISON OF THE TEXT

06 February 2025