PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

TERALAVID (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.

Each tablet contains sugar (mannitol 134,28 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Tablets are light orange coloured, round shaped, biconvex, film coated tablets debossed with “LA54” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TERALAVID is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral medicines in adults aged 18 years and older.

4.2 Posology and method of administration

Posology:

TERALAVID therapy should be initiated by a medical practitioner experienced in the management of HIV infection. TERALAVID can be taken with or without food.

Adults:

Treatment-naïve:

For patients initiating antiretroviral therapy for the first time (treatment-naïve), the recommended dose of TERALAVID is 50 mg once daily.

Treatment-experienced, and integrase inhibitor naïve:

For patients who are treatment experienced and have not previously been treated with an integrase inhibitor, the recommended dose of TERALAVID is 50 mg once daily.

Integrase inhibitor resistant:

For patients with integrase inhibitor resistance, the recommended dose of TERALAVID is 50 mg twice daily.

Elderly:

There are limited data available on the use of TERALAVID in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2, Special Patient Populations).

Renal impairment:

No dosage adjustment is required in patients with mild, moderate or severe (CrCl < 30 ml/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis, although differences in pharmacokinetics are not expected in this population (see section 5.2, Special Patient Populations).

Treatment with dolutegravir has been found to result in an early small increase of mean serum creatinine levels by 10-14 %, which was found to remain stable over time and is not considered clinically relevant (see section 4.8).

Hepatic impairment:

No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh grade A or B).

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

Paediatrics

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

Method of administration

For oral use.

TERALAVID film-coated tablets must be swallowed whole with water. Film-coated tablets must not be crushed or chewed. TERALAVID may be taken with or without food.

4.3 Contraindications

TERALAVID is contraindicated in patients with known hypersensitivity to dolutegravir or to any of the excipients.

TERALAVID is contraindicated in combination with dofetilide and pilsicainide.

TERALAVID is contraindicated in moderate and severe hepatic impairment.

Metformin is contraindicated in patients taking TERALAVID.

TERALAVID is contraindicated in the first trimester of pregnancy.

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, the active component of TERALAVID, and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue TERALAVID 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. A delay in stopping treatment with TERALAVID or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy (cART) has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Syndrome:

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

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see section 4.8).

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). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Hepatic impairment:

The unbound fraction of TERALAVID in the blood is doubled in patients with moderate hepatic impairment.

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

Interactions:

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

The co-administration of TERALAVID with etravirine (ETR) is not recommended, unless the patient is

also receiving concomitant atazanavir and ritonavir (ATV + RTV), lopinavir and ritonavir (LPV + RTV) or darunavir and ritonavir (DRV + RTV) (see section 4.5).

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

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

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

Co-infection with Hepatitis B or C:

Overall, the safety profile of dolutegravir (the active component of TERALAVID) in patients co-infected with hepatitis B and/or C was similar to that reported in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were reported in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Monitoring of liver chemistry is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see section 4.8).

Opportunistic infections:

Patients receiving TERALAVID or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV

diseases. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including TERALAVID, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Excipients with known effects:

Each tablet of TERALAVID contains approximately 4,08 mg sodium (found in table salt), which is below 1 mmol/dose (23 mg) and as such may be regarded as being essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

Effect of TERALAVID on the pharmacokinetics of other medicines:

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50} > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2. *In vitro,* dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on this data, TERALAVID 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 medicine 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 inhibited the renal organic cation transporter 2 (OCT2). Based on this report, TERALAVID may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see section 4.3 and Table 1: Medicine Interactions - Other Medicines).

Effect of other medicines on the pharmacokinetics of TERALAVID:

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

Co-administration of TERALAVID and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase the plasma concentration of TERALAVID (see Table 1).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and thus require a TERALAVID dose adjustment to 50 mg twice daily.

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

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 TERALAVID 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 TERALAVID. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 1: 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, bocepravir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no TERALAVID dose adjustment is required when co-administered with these medicines.

Table 1: 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. TERALAVID 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 TERALAVID 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 TERALAVID 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.
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 TERALAVID 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	Dolutegravir↓ AUC↓ 35 %	Fosamprenavir/ ritonavir decreases dolutegravir concentrations, but based on

(FPV + RTV)	C_{max}↓ 24 % C_T↓ 49 % FPV↔ RTV↔	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 % DRV↔ RTV↔	Darunavir/ritonavir did not change dolutegravir plasma concentrations 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 clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir↔ AUC↑ 10 % C_{max}↑ 7 % C_T↑ 28 %	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

	LPV↔ RTV↔ 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 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 TERALAVID is contra-indicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort	Dolutegravir↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co- administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g. Mg, Al or Ca)	Dolutegravir↓ AUC↓ 74 % C_{max}↓ 72 % C_{24}↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. TERALAVID 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 %	TERALAVID 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 %	TERALAVID 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 contra- indicated in patients taking TERALAVID (see section 4.3).
Rifampicin	Dolutegravir↓ AUC↓ 54 % C_{max}↓ 43 % C_T↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of TERALAVID 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 %	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 TERALAVID.

	C_{max}↓ 11 % C_T↓ 7 %	
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 TERALAVID.

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.

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 TERALAVID (see below), including consideration of using effective contraceptive measures.

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

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with TERALAVID 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 TERALAVID, 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.

TERALAVID 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 breastfeed their infants in order to avoid transmission of HIV. Dolutegravir is excreted in human breast milk, and there is significant exposure to the neonate/infant due to slow elimination; the half-life of dolutegravir in the newborn was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

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

TERALAVID can cause undesirable effects (including headache, dizziness, fatigue), which may affect the ability to drive and operate machines.

Patients should be advised not to engage in driving or operating machines until they know how TERALAVID might affect them.

4.8 Undesirable effects

Immune system disorders:

Less frequent: Hypersensitivity (see section 4.4), Immune Reconstitution Syndrome (see section 4.4).

Psychiatric disorders:

Frequent: Insomnia.

Frequency unknown: Anxiety.

Nervous system disorders:

Frequent: Headache, dizziness, abnormal dreams.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain.

Less frequent: Abdominal pain, abdominal discomfort.

Hepato-biliary disorders:

Frequent: Hepatitis.

Frequency unknown: Acute liver failure, hepatotoxicity.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus.

Musculoskeletal and connective tissue disorders:

Frequency unknown: Arthralgia, myalgia.

General disorders and administration site conditions:

Frequent: Fatigue.

Investigations:

Frequency unknown: Weight increased.

Changes in laboratory chemistries:

Increases in serum creatinine occurred within the first week of treatment with dolutegravir (the active component of TERALAVID) and remained stable through 48 weeks. In treatment naïve patients a mean change from baseline of 9,96 µmol/l (range: -53 µmol/l to 54,8 µmol/l) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment experienced patients. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see section 5.1, Effects on renal function).

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir and raltegravir (but not efavirenz) arms in the programme. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see section 5.2 (Metabolism)).

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy.

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 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: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antivirals for systemic use, Direct acting antivirals, Integrase inhibitors, ATC code: J05AJ03

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 ($t_{1/2}$ 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 substitution observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wildtype subtype B, C and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

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

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

Integrase Inhibitor-Resistant HIV-2 Strains: Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure.

Overall the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Clinical isolates from raltegravir treatment virologic failure subjects: 705 raltegravir resistant clinical isolates were analysed for susceptibility to dolutegravir using the Monogram Biosciences Phenosense assay. Dolutegravir has a <10 FC against 93,9 % of the 705 clinical isolates.

Resistance *in vivo:* integrase inhibitor naïve patients:

No integrase inhibitor (INI) resistant mutations or treatment-emergent resistance to NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment-naïve studies (SPRING-1, SPRING-2 and SINGLE studies). In the SAILING study for treatment experienced (and integrase naïve) patients (n = 354 in the dolutegravir arm), treatment-emergent integrase resistance was observed in 2 of 9 subjects with virologic failure. In both cases, a unique R263K integrase substitution was observed, with a maximum FC of 1,93.

Resistance *in vivo*: integrase inhibitor resistant patients:

The VIKING-3 study examined dolutegravir (plus optimised background therapy) in subjects with pre-existing INI resistance. Twenty-six subjects (26/114) experienced protocol defined virologic failure through to week 24. Of these, 25 had paired baseline and PDVF resistance data for analysis and 13/25 (52 %) had treatment-emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were E92Q (n = 2), T97A (n = 6), E138K/A (n = 4), G140S (n = 2), Y143H (n = 1), S147G (n = 1), Q148H/K/R (n = 3), and N155H (n = 1). Eleven of the 13 subjects with virus exhibiting treatment emergent mutations harboured Q148 pathway virus present at baseline or historically.

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 in an open-label, randomised, 3 arm, parallel, placebo-controlled study in 37 healthy subjects, who were administered dolutegravir 50 mg once daily (n = 12), 50 mg twice daily (n = 13) or placebo once daily (n = 12) for 14 days. A small decrease of 10-14 % in mean serum

creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

5.2 Pharmacokinetic properties

Pharmacokinetic properties:

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

Absorption:

Dolutegravir is absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for the tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, dolutegravir exhibited non-linear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however, increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 34 %, 41 %, and 66 %, increased C_{max} by 46 %, 52 % and 67 %, and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.

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 drug-related radioactivity concentration ratios averaged between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects, approximately 0,4 to 0,5 % in subjects with moderate hepatic impairment and 0,8 to 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects 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 section 5.1).

Metabolism:

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

Special patient populations:

Adolescents:

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

Due to lack of clinical data, dolutegravir, as in TERALAVID, is not recommended for use in patients under 18 years of age (see section 4.2).

Table 2: Adolescent pharmacokinetic parameters

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

[a] One subject weighing 37 kg received 35 mg once daily

Elderly:

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

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

Renal impairment:

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CL_{CR} < 30 ml/min). No clinically important pharmacokinetics differences between subjects with severe renal impairment (CL_{CR} < 30 ml/min) and matching healthy subjects were observed; AUC, C_{max}, and C_{24} if dolutegravir were decreased by 40 %, 23 % and 43 %, respectively, compared with those in matched healthy subjects. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment:

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is necessary for patients with mild hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in metabolising enzymes:

There is no evidence that common polymorphisms in metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32 % lower clearance of dolutegravir and 46 % higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41). Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with Hepatitis B or C:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TERALAVID contains mannitol, microcrystalline cellulose, povidone K 30, sodium starch glycolate and sodium stearyl fumarate. The tablets are film-coated with a coating material containing FD&C YELLOW #6, polyethylene glycol 3350, polyvinyl alcohol, talc and titanium dioxide.

6.2 Incompatibilities

Not applicable (e.g. solid oral pharmaceutical forms).

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C in the original container.

Keep the container tightly closed.

After first opening, store at or below 25 °C in the original container and use within 30 days (28's and 30's tablets) or 90 days (84's and 90's tablets) after first opening.

STORE ALL MEDICINES OUT OF REACH AND SIGHT OF CHILDREN.

6.5 Nature and contents of container

Containers of 28's: TERALAVID is packed in white 60 cc HDPE bottles with 33 mm child resistant screw caps containing 28 tablets.

Containers of 30's: TERALAVID is packed in white 60 cc HDPE bottles with 33 mm child resistant screw caps containing 30 tablets.

Containers of 84's: TERALAVID is packed in white 85 cc HDPE bottles with 33 mm child resistant screw caps containing 84 tablets.

Containers of 90's: TERALAVID is packed in white 85 CC HDPE bottle with 33 mm child resistant cap containing 90 tablets.

6.6 Special precautions for disposal and other handling

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Umsebe Healthcare

506 Sunclare Building

21 Dreyer Street, Claremont

Cape Town

7708

South Africa

8. REGISTRATION NUMBER

58/20.2.8/0005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 September 2024

10. DATE OF REVISION OF THE TEXT

17 September 2024

Namibia:	Reg No.: TBA	NS2