Proposed Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

[PRODUCT NAME]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Dolutegravir Sodium equivalent to

Dolutegravir 50 mg.

Contains sugar: 144,4 mg mannitol

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

Light brown to brown film coated, caplet shaped tablets debossed

441. with “RL75” on one side and breakline on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[PRODUCT NAME] 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

[PRODUCT NAME] therapy should be initiated by a medical practitioner

experienced in the management of HIV infection. **[PRODUCT NAME]** can be taken with or without food.

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking **[PRODUCT NAME]**.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in **[PRODUCT NAME]**.

Adults:

Treatment-naive:

For patients initiating antiretroviral therapy for the first time (treatment-naive) the recommended dose of **[PRODUCT NAME]** 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 **[PRODUCT NAME]** is 50 mg once daily.

Integrase inhibitor resistant:

For patients with integrase inhibitor resistance, the recommended dose of **[PRODUCT NAME]** is 50 mg twice daily.

Elderly:

There are limited data available on the use of **[PRODUCT NAME]** 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 reported in subjects receiving dialysis, although differences in pharmacokinetics are not expected in this population (see section 5.2 - Special Patient Populations).

Treatment with **[PRODUCT NAME]** resulted in an early small increase of

mean serum creatinine levels by 10-14 % which remained 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). **[PRODUCT NAME]** is contra-**i**ndicated in patients with moderate or severe hepatic impairment (see section 4.3).

4.3 Contraindications

- **[PRODUCT NAME]** is contraindicated in patients with known hypersensitivity to dolutegravir or to any of the excipients.
- **[PRODUCT NAME]** is contraindicated in moderate and severe hepatic
- impairment.
- **[PRODUCT NAME]** is contraindicated in combination with dofetilide and pilsicainide.
- Metformin is contraindicated in patients taking **[PRODUCT NAME].**

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including **[PRODUCT NAME]** and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury.

Discontinue **[PRODUCT NAME]** 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 **[PRODUCT NAME]** or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy 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 Inflammatory Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious

clinical conditions, or aggravation of symptoms. Typically, such reactions have been reported within the first few weeks or months of initiation of ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal atypical mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

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.

Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Liver chemistry elevations consistent with immune reconstitution syndrome were reported in some hepatitis B and/or C co-infected patients at the start of **[PRODUCT NAME]** therapy. Monitoring of liver chemistries isrecommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied ininitiating 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.

Opportunistic infections

Patients receiving **[PRODUCT NAME]** should be advised that they may

continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. 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 **[PRODUCT NAME]**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Hepatic impairment:

The unbound fraction of dolutegravir in the blood is doubled in patients with moderate hepatic impairment. **[PRODUCT NAME]** is contra-indicated 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 **[PRODUCT NAME]** or medicines that may have their exposure changed by **[PRODUCT NAME]** (see section 4.3 and 4.5).

The co-administration of **[PRODUCT NAME]** with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV + RTV) (see section 4.5).

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

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

Metformin concentrations may be increased by **[PRODUCT NAME]**.

Metformin is contraindicated in patients taking **[PRODUCT NAME]** (see section 4.3).

Co-infection with Hepatitis B or C:

Overall, the safety profile 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 **[PRODUCT NAME]** therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Opportunistic infections:

Patients receiving **[PRODUCT NAME]** 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.

4.5 Interaction with other medicines and other forms of interaction

Effect of [PRODUCT NAME] on the Pharmacokinetics of Other

medicines:

In vitro, 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

has been reported with dolutegrivir, as contained in **[PRODUCT NAME]**.

Dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. /*n vivo,* dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these reported data, **[PRODUCT NAME]** 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).

[PRODUCT NAME] 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.

It was reported that dolutegravir inhibited the renal organic cation transporter 2 (OCT2). Dolutegravir may therefore increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide,metformin) (see **Table 2: Medicine Interactions - Other Medicines**).

Effect of Other Medicines on the Pharmacokinetics of

[PRODUCT NAME]:

All factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance.

[PRODUCT NAME] is eliminated mainly through metabolism by UGT1A1.

[PRODUCT NAME] 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 **[PRODUCT NAME]**.

Co-administration of **[PRODUCT NAME]** and other medicines that inhibit:UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see **Table 2**).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require **[PRODUCT NAME]** 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 **[PRODUCT NAME]** 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 **[PRODUCT NAME]**. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see **Table 2:.Medicine Interactions- HIV-1 Antiviral Medicines**). It was reported that 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 **[PRODUCT NAME]** dose adjustment is required when co-administered with these medicines.

Table 2: Medicine interactions

Concomitant Medicine Class: Medicine	**Effect on Concentration of [PRODUCT NAME] or Concomitant Medicine**	**Clinical Comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC↓ C_{max} ↓ Ct ↓ ETR ↔	Etravirine decreased dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. **[PRODUCT NAME]** 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 ↓ C_{max} ↓ Ct ↓ EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of **[PRODUCT NAME]** 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. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz.The recommended dose of **[PRODUCT NAME]** 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 ↑ C_{max} ↑ Ct ↑ ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV+RTV)	Dolutegravir ↑ AUC ↑ C_{max} ↑ Ct ↑ ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.

Protease Inhibitor: Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ C_{max} ↓ Ct ↓ TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of **[PRODUCT NAME]** is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Fosamprenavir/ritonavir (FPV+RTV)	Dolutegravir↓ AUC ↓ C_{max}↓ Ct ↓ FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in reported phase Ill 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 reported. 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}↔ Ct ↔	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 ↓ C_{max}↓ Ct ↓ 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 ↑ C_{max}↑ Ct↑ LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir +Etravirine (DRV/RTV+ETR)	Dolutegravir↓ AUC ↓ C_{max}↓ Ct↓ 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 **[PRODUCT NAME]** is contraindicated due to the potential life threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbitone Carbamazepine St. John's wort	Dolutegravir↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC ↓ C_{max} ↓ C_{24} ↓	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. **[PRODUCT NAME]** is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.

Calcium supplements	Dolutegravir ↓ AUC ↓ C_{max} ↓ C_{24} ↓	**[PRODUCT NAME]** 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 ↓ C_{max} ↓ C_{24}↓	**[PRODUCT NAME]** is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking **[PRODUCT NAME]** (see section 4.3)
Rifampicin	Dolutegravir ↓ AUC ↓ C_{max}↓ Ct ↓	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of **[PRODUCT NAME]** 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 ↑ C_{max}↓ Ct ↑ Effect of dolutegravir: NGMN ↔ AUC ↓ C_{max} ↓ Ct ↓	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 **[PRODUCT NAME]**.

Methadone	Effect of dolutegravir: Methadone↔ AUC ↓ C_{max} ↔ Ct ↓	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with **[PRODUCT NAME]**.
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.		

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 **[PRODUCT NAME]** in women of childbearing potential to exclude inadvertent (unintentional) use of **[PRODUCT NAME]** 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.

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

The clinical status of the patient and the adverse event profile of **[PRODUCT NAME]** should be borne in mind when considering the patient's ability to drive or operate machinery.

[PRODUCT NAME] may affect the ability to drive and use machines. Patients should ensure that they do not engage in driving or operating

machines until they know how **[PRODUCT NAME]** affects them.

4.8 Undesirable effects

Immune system disorders	Less frequent	Hypersensitivity (see section 4.4)
	Less frequent	Immune Reconstitution Syndrome (see section 4.4)
Psychiatric disorders	Frequent	Insomnia
	Frequent	Depression
	Frequent	Headache

Nervous system disorders	Frequent	Dizziness
	Frequent	Abnormal dreams
Gastrointestinal disorders	Frequent	Nausea
	Frequent	Diarrhoea
	Frequent	Vomiting
	Frequent	Flatulence
	Frequent	Upper abdominal pain
	Less frequent	Abdominal pain
	Less frequent	Abdominal discomfort
Hepatobiliary disorders	Less frequent	Hepatitis
Skin and subcutaneous tissues	Frequent	Rash
	Frequent	Pruritus
General disorders and administration site conditions	Frequent	Fatigue
Investigations	Frequent	Increased AST, ALT, CPK, bilirubin

The safety profile was reported to be similar across the treatment naïve, treatment experienced (and integrase naïve) and integrase resistant patient populations.

Description of changes in laboratory chemistry:

Increases in serum creatinine: Increases in serum creatinine occurred within the first week of treatment with **[PRODUCT NAME]** 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 reported 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).

Increases in total bilirubin: Small increases in total bilirubin (without clinical jaundice) were reported with **[PRODUCT NAME]** and raltegravir (but not efavirenz). These changes are not considered clinically relevant

as they likely reflect competition between **[PRODUCT NAME]** and unconjugated bilirubin for a common clearance pathway (UGT1A1) [see section 5.2- Metabolism].

Increase in creatine phosphokinase (CPK): Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with **[PRODUCT NAME]** therapy.

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 provders 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 **[PRODUCT NAME]**. If

overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As **[PRODUCT NAME]** 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

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 were not reported during HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir, integrase substitutions reported 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 wildtype strain.

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

Integrase Inhibitor-Resistant HIV-2 Strains: Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who reported virologic failure. Overall the HIV-2 FCs reported were similar to HIV-1 FCs observed for similar pathway mutations.

Clinical Isolates From Raltegravir Treatment Virologic Failure Subjects:

Seven hundred and five raltegravir resistant clinical isolates were reported to be analyzed for susceptibility to dolutegravir using the Monogram Biosciences PhenoSense assay. It has been reported that 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 the NRTI backbone therapy were reported with dolutegravir 50 mg once daily in treatment-naïve patients. In treatment experienced

(and integrase naïve) patients, treatment emergent integrase resistance was reported with virologic failure. In those cases, a unique R263K integrase substitution was reported, with a maximum FC of 1,93.

Resistance *in vivo:* integrase inhibitor resistant patients:

In subjects with pre-existing INI resistance, treatment emergent mutations or mixtures of mutations reported were E92Q, T97A , E138K/A, G140S, Y143H, S147G , Q148H/K/R and N155H. 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 (CrCI), 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 healthy subjects, who were administered dolutegravir 50mg once daily, 50 mg twice daily or placebo once daily for 14 days. A small decrease of 10-14 % in mean

serum creatinine clearance (CrCI) was reported 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). It was reported 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

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. The between-subject PK variability of dolutegravir was reported to be 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-∞) and C_{max} and also prolonged T_{max}. These increases are not clinically significant.

The absolute bioavailability of dolutegravir has not been reported.

Distribution:

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is reported at 12,5 L.

Binding of dolutegravir to plasma proteins was independent of concentration. 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 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 baselinein 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. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the

glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose).

Eliminatlon:

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

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

*One subject weighing 37 kg received 35 mg once daily

Table 1: Adolescent pharmacokinetic parameters

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

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. No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCl< 30 ml/min) and healthy subjects were reported. 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. Exposure of 50 mg dose dolutegravir was reported to be similar between subjects with moderate hepatic impairment (Child-Pugh category B) and healthy individuals. No dosage adjustment is necessary for patients with mild hepatic impairment. The effect of

severe hepatic impairment on the pharmacokinetics of dolutegravlr 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 reported clinical studies in healthy subjects, subjects with UGT1A 1 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 UGT1A 1. Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with Hepatitis B or C:

It was reported that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data reported on subjects with hepatitis B co-infection.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Magnesium stearate
- Mannitol
- Microcrystalline cellulose
- Povidone
- Sodium starch glycollate
- Sodium stearyl fumarate
- Talc

Coating material: opadry II (brown)

- Iron oxide yellow
- Iron oxide red
- Macrogol/Peg
- Polyvinyl Alcohol-Part- hydrolyzed
- 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. Keep well closed. Protect from moisture.

6.5 Nature and contents of container

The tablets are packed in HDPE Bottles containing 28,30 and 90

Tablets. HDPE Bottles can be supplied with or without 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, 1724

South Africa

8. REGISTRATION NUMBER(S)

VIDOTEG: 53/20.2.8/0181

TEDOTIG: 53/20.2.8/0182.181

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 February 2020

10. DATE OF REVISON OF THE TEXT

07 February 2022