Approved Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MYLTEGA

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains: mannitol

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

A pink, film-coated, round, biconvex, bevelled edge tablet debossed with M on one side of the tablet and DT5 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology:

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

MYLTEGA can be taken without food.

Method of Administration:

Adults:

Treatment-naïve:

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

Integrase inhibitor resistant:

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

Elderly:

There are limited data available on the use of MYLTEGA in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients.

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.
Treatment with MYLTEGA 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). MYLTEGA **is** contra-indicated in patients with moderate or severe hepatic impairment (see section 4.3).

Co-administration with other medicines (see section 4.4 interactions and Table 1.)

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking MYLTEGA. (see section 4.4)
There is evidence that the concentration of isoniazid is increased by dolutegravir as contained in MYLTEGA. (see section 4.4)

4.3 Contraindications

- Hypersensitivity to dolutegravir or any of the inactive ingredients of MYLTEGA (see section 6.1).
- MYLTEGA is contraindicated in combination with dofetilide and pilsicainide.
- MYLTEGA is contraindicated in moderate and severe hepatic impairment.
- Metformin is contraindicated in patients taking MYLTEGA.
- In the peri-conception period and the first trimester of pregnancy
- Safety in pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including MYLTEGA and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue MYLTEGA and other suspect medicines immediately if signs or symptoms of hypersensitivity reaction 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 MYLTEGA 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 distribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution 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 observed 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. Auto-immune disorders (such as Graves' disease, polymyositis and Guillian-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 observed in some hepatitis B and/or C co-infected patients at the start of MYLTEGA 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 dolutegravir in the blood is doubled in patients with moderate hepatic impairment. MYLTEGA is contra-indicated in patients with moderate to severe hepatic impairment (see section 4.3).

Interactions:

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

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

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

Metformin concentrations may be increased by MYLTEGA. Metformin is contra-indicated in patients taking MYLTEGA (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 observed 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 for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of MYLTEGA therapy, particularly in those anti-hepatitis B therapy was withdrawn.

Opportunistic infections:

Patients receiving MYLTEGAor 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.

Transmission of infection:

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

Important information about some of the ingredients of MYLTEGA

MYLTEGA tablets contain mannitol, which may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Effect of MYLTEGA on the Pharmacokinetics of Other medicines:

In vitro, MYLTEGAdemonstrated no direct, or weak inhibition (IC50 > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19,CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 Or UGT2B7, or the transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2.

In vitro, dolutegravir did not induce CYP1A2, CYP2B6 OR CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, MYLTEGA 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 studies, MYLTEGA did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.
In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OTC2). Based on this observation, MYLTEGA may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see Table 1: Medicine Interactions-Other medicines).
Therefore the OTC2 inhibitors are contraindicated with the use of MYLTEGA**.**

Effect of Other medicines on the Pharmacokinetics of MYLTEGA:
MYLTEGA is eliminated mainly through metabolism by UGT1A1. MYLTEGA 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 MYLTEGA. Co-administration of MYLTEGAand other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 1).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require MYLTEGA 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 MYLTEGA 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 MYLTEGA. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 1: Medicines Interactions- HIV-1 Antiviral medicines). A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no MYLTEGA dose adjustment is required when co-administered with these medicines.

Table 1: Medicine Interactions

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of MYLTEGA or Concomitant Medicine**	**Clinical comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reserve 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. MYLTEGA 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 MYLTEGA 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 MYLTEGA 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 concentrations. 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 in necessary.
Protease inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47% C_T↓ 76 % TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of MYLTEGA is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.
Protease inhibitor: Fosamprenavir/ritonavir (FPV + RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24% C_T↓ 49 % FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include Fosamprenavir/ritonavir should be used where possible in INI resistant patients.
Protease inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on

		data from other inhibitors, an increase is not expected. No dose adjustment is necessary
Protease inhibitor: Lopinavir/ ritonavir (LPV + RTV)	DTG ↔ AUC ↔ C_{max} ↔ C_{τ} ↔ 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_{τ}↓ 38 % DRV ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reserve 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_{τ} ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease inhibitor:	Dolutegravir ↓ AUC ↓ 25 %	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a

Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	C_{max} ↓ 12 % C_T↓ 36 % DRV ↔ RTV ↔	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 MYLTEGA is contra-indicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbitone Carbamazepine St. John's wort	Dolutegravir ↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cation decreased dolutegravir plasma concentration. MYLTEGA 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 %	MYLTEGA 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 %	MYLTEGA 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 MYLTEGA (see section 4.3)
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_{T}↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of MYLTEGA 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 %	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 MYLTEGA.

	Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % 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 MYLTEGA.

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

Perform pregnancy testing before initiation of MYLTEGA in women of childbearing potential to exclude inadvertent (unintentional) use of MYLTEGA 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.

Breast-feeding:

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The undesirable effects are listed by system organ classes.

Immune system disorders:

Less frequent: Hypersensitivity, Immune Reconstitution Syndrome

Psychiatric disorders:

Frequent: Insomnia, abnormal dreams, depression, anxiety

Less frequent: Suicidal ideation or suicide attempt

Nervous system disorders:

Frequent: Headache, dizziness

Gastrointestinal disorders:

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

Less frequent: Abdominal pain, abdominal discomfort

Hepatobiliary disorders:

Frequent: Hepatitis

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus

Musculoskeletal and connective tissue disorders:

Less frequent: Arthralgia, myalgia.

General disorders and administration site conditions:

Frequent: Fatigue

Investigations:

Frequent: Increased AST, ALT, CPK, bilirubin

Changes in laboratory chemistries:

Increases in serum creatinine occurred within the first week of treatment with MYLTEGA 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.

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

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with MYLTEGA 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. 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: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms may be an exacerbation of side effects.

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 MYLTEGA. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As MYLTEGA 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: Antivirals for systemic use, other antivirals,

ATC code: J05AX12

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t½ 71 hours).

Resistance in vitro:

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir were not observed during HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir integrase substitutions observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wildtype subtype B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R and S153T.

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

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

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

Clinical Isolates From Raltegravir Treatment Virologic Failure Subjects: Seven hundred and five 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 the 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 mutations harboured Q148 pathway virus present at baseline or historically.

5.2 Pharmacokinetic properties

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

Absorption

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

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increased dolutegravir AUC $(0 - \infty)$ 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 clinically significant.

The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on *in vitro* data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12,5 L. Binding of dolutegravir to plasma was independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects, approximately 0,4 to 0,5 % in subjects with moderate hepatic impairment, and 0,8 to 1,0 % in subjects with severe renal impairment and 0,5% in HIV-1 infected patients. Dolutegravir is present in cerebrospinal fluid (CSF). 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 IC50); CSF: plasma concentration ratio of dolutegravir ranged from 0,11 to 0,66 %. Dolutegravir concentrations in CSF exceeded the IC50, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy (see Pharmacodynamic properties).

Metabolism

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose).

Elimination

Dolutegravir has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 0,56 L/hr.

Special patient populations:

Adolescents:

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to < 18 years of age) showed that dolutegravir 50 mg once daily

dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 mg once daily.

Due to lack of clinical data, dolutegravir, as in TIVCAY, 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 (CLcr < 30 mLmin). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 mL/min) and matching healthy subjects were observed, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 %, and 43 %, respectively, compared with those in matched healthy subjects. No dosage adjustment is

necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment:

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B) 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

The other ingredients of MYLTEGA are:

Tablet core: Microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate.

Tablet coating: Black iron oxide/ferrosoferric oxide, iron oxide red, macrogol, polyvinyl alcohol, talc, titanium dioxide.

Contains sugar (Mannitol 145,4 mg).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the tablets in the original container until required for use.

6.5 Nature and contents of container

HDPE Container pack:

MYLTEGA tablets are packed in blue opaque, high density polyethylene (HDPE) bottles with a blue opaque polypropylene cap.

The HDPE bottle is packed into an outer cardboard carton.

Pack size:

30’s – One HDPE container contains 30 tablets.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

4 Brewery Street

Isando

1609

Republic of South Africa

8 REGISTRATION NUMBER

52/20.2.8/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine.

10 DATE OF REVISION OF THE TEXT

05/04/2022