PROFESSIONAL INFORMATION

DALIMUNE

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

DALIMUNE Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DALIMUNE film coated tablet contains 50 mg of dolutegravir (as dolutegravir sodium).

Contains sugar: mannitol 145,00 mg/tablet.

For full list of excipients, see **section 6.1.**

3 PHARMACEUTICAL FORM

Film coated tablet

Brown coloured round shaped biconvex film coated tablet debossed with “C 50” on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DALIMUNE is indicated in combination with other anti-retroviral medicines for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 18 years of age.

4.2 Posology and method of administration

Posology

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

DALIMUNE 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 DALIMUNE is 50 mg once daily.

DALIMUNE should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz; nevirapine tipranavir/ritonavir; or rifampicin) (see **section 4.5**).

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 DALIMUNE is 50 mg once daily.

Integrase inhibitor resistant

For patients with integrase inhibitor resistance, the recommended dose of DALIMUNE is 50 mg (one tablet) twice daily.

Co-administration of DALIMUNE with some medicines should be avoided in this population (e.g. efavirenz; nevirapine tipranavir/ritonavir; or rifampicin) (see **section 4**.4 and **section 4.5**).

Special populations

Elderly

There are limited data available on the use of dolutegravir as in DALIMUNE 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 5.1 –** 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 5.1 –** Special patient populations).

Treatment with DALIMUNE may result in an early small increase in mean serum levels by 10-14 % which may remain stable over time and is not clinically significant.

Method of administration

DALIMUNE is for oral administration and should be swallowed whole.

4.3 Contraindications

DALIMUNE is contraindicated in combination with dofetilide and pilsicainide.

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

DALIMUNE is contraindicated in moderate and severe hepatic impairment.

Metformin is contraindicated in patients taking DALIMUNE.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity reactions have been reported with integrase inhibitors, including DALIMUNE and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue DALIMUNE 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 DALIMUNE 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

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.

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 DALIMUNE 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 DALIMUNE, 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. DALIMUNE is contraindicated in patients with moderate or severe hepatic impairment (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 is similar to that observed in patients without Hepatitis B and/or C co-infection, although the rates of AST and ALT abnormalities are higher in subgroup with Hepatitis B and/or C co-infection. Liver chemistry elevations consistent with immune reconstitution syndrome are observed in some patients with Hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy is withdrawn.

Changes in Laboratory chemistries

Increases in serum creatinine may occur within the first week of treatment with DALIMUNE and remain 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) may be observed after 48 weeks of treatment. Creatinine increases may be comparable by background NRTIs and may be similar in treatment experienced patients. As these changes do not reflect a change in the glomerular filtration rate (see **section 5.1** – Effects on Renal Function), it is not considered to be clinically relevant.

Small increases in bilirubin (without clinical jaundice) may be observed with DALIMUNE and raltegravir (but not efavirenz). These changes are not considered clinically relevant as they may reflect competition between DALIMUNE and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see **section 5.1** – Metabolism).

Asymptomatic creatinine phosphokinase (CPK) elevations mainly in association with exercise may occur with DALIMUNE.

DALIMUNE contains mannitol and may have a laxative effect**.**

4.5 Interaction with other medicines and other forms of interaction

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

Co-administration of dolutegravir may potentially increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter. Co-administration has not been studied. Dofetilide or pilsicainide co-administration with DALIMUNE is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see **section 4.3**).

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

The co-administration of DALIMUNE 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)

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

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

Effect of DALIMUNE on the pharmacokinetics of other medicines

In vitro, DALIMUNE demonstrated no direct, or weak inhibition (IC50 > 50 μM) of the enzymes cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, DALIMUNE 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, DALIMUNE 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 observation, DALIMUNE may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, pilcicainide, metformin). Therefore, these OCT2 inhibitors are contraindicated for use with DALIMUNE (see **section 4.3** and **Table 1**: Medicine interactions – Other medicines).

Effect of other medicines on the pharmacokinetics of DALIMUNE:

DALIMUNE is eliminated mainly through metabolism by UGT1A1. DALIMUNE 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 DALIMUNE.

Co-administration of DALIMUNE and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration.

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

DALIMUNE 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 DALIMUNE. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table1: Medicine Interactions – HIV-1 Antiviral Medicines). A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no DALIMUNE dose adjustment is required when co-administered with these medicines.

Table 1: Medicine Interactions

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; Cmax = maximum observed concentration, Cτ = concentration at the end of dosing interval.

Medicines by therapeutic classes	**Interaction Geometric mean change (%)**	**Recommendation concerning co-administration**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % Cτ ↓88 % ETR ↔	Etravirine may decrease dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. DALIMUNE 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 % Cτ ↓ 75 % EFV ↔	Efavirenz may decrease dolutegravir plasma concentrations. The recommended dose of DALIMUNE 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. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered (see **section 4.4**).
Protease Inhibitor: Darunavir/ritonavir + and etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % Cτ ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine may not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary
Rilpivirine	Dolutegravir ↔ AUC ↑ 12 % C_{max} ↑ 13 % Cτ ↑ 22 % Rilpivirin ↔	No dose adjustment is necessary
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDV)	Dolutegravir ↔ TDV ↔	Tenofovir may not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary

Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 49 % Cτ ↑ 180 % ATV ↔	Atazanavir may increase dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + and etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑ 10 % C_{max} ↑ 7 % Cτ ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine may not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary
Protease Inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % Cτ ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir may increase dolutegravir plasma concentration. No dose adjustment is necessary.

Protease Inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % Cτ ↓ 76 % TPV ↔ RTV ↔	Tipranavir/ritonavir may decrease dolutegravir concentrations. The recommended dose of DALIMUNE is 50 mg twice daily when co-administered with tipranavir/ ritonavir. In the presence of integrase class resistance this combination should be avoided.
Protease Inhibitor: Fosamprenavir/ ritonavir (FPV + RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % Cτ ↓ 49 % TPV ↔ RTV ↔	No dose adjustment is necessary in the absence of integrase class resistance. In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Protease Inhibitor: Nelfinavir	Dolutegravir ↔	Although an inhibitor of CYP3A4, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 32 % C_{max} ↓ 11 % Cτ ↓ 38 % DRV ↔ RTV ↔	Darunavir/ritonavir may not change dolutegravir concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV + RTV)	DTG ↔ AUC ↔ C_{max} ↔ Cτ ↔ LPV ↔ RTV ↔	Lopinavir/ritonavir may not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Other Antiviral Medicines		
Telaprevir	Dolutegravir ↑ AUC ↑ 25 % C_{max} ↑ 19 % Cτ ↑ 37 % Telapevir ↔ (Historical controls) (Inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Boceprevir	Dolutegravir ↔ AUC ↑ 7 % C_{max} ↑ 5 % Cτ ↑ 8 % Boceprevir ↔ (Historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33 % C_{max} ↑ 29 % Cτ ↑ 45 % Boceprevir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.
Other Medicines		
Antidysrhythmics		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir may increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter. Dolutegravir and dofetilide or pilsicainide co-administration is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see **section 4.3**).
Anticonvulsants		

Carbamazepine	Dolutegravir ↓ AUC ↓ 49 % C_{max} ↓ 33 % Cτ ↓ 73 %	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. Alternative to carbamazepine should be used where possible for INI resistant patients.
Oxcarbazepine Phenytoin Phenobarbitone	Dolutegravir↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected).	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. Alternative combinations that do not include these metabolic inducers should be used where possible for INI resistant patients.
Azole anti-fungal medicines		
Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, marked increase is not expected.
Herbal products		
St. John`s wort	Dolutegravir↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with St. John`s wort. Alternative combinations that do not include St. John`s wort should be used where possible for INI resistant patients.
Antacids and supplements		

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 may decrease dolutegravir concentration. Antacids containing polyvalent cations should be taken well separated in time from administration of dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before)
Iron supplements	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 57 % C_{24} ↓ 56 %	
Multivitamin	Dolutegravir ↓ AUC ↓33 % C_{max} ↓ 35 % C_{24} ↓ 32 % Complex binding to polyvalent ions	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11 % C_{max} ↑ 6 % Cτ ↑ 17 %	No dose adjustment is necessary.
Antidiabetics		

Metformin	Metformin ↑	Co-administration of dolutegravir may increase plasma concentration. Metformin is contraindicated in patients taking DALIMUNE (see **section 4.3**).
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % Cτ ↓ 72 %	Rifampicin may decrease dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI resistant patients.
Rifabutin	Dolutegravir ↔ AUC ↓ 5 % C_{max} ↑ 16 % Cτ ↓ 30 % (Induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Oral contraceptives		
Ethinyl oestradiol (EE) and Norelgestromin (NGMN)	Effect of dolutegravir EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % Cτ ↑ 2 % Effect of dolutegravir NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % Cτ ↓ 7 %	Dolutegravir may not change ethinyl oestradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with DALIMUNE.

Analgesics		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % Cτ ↓ 1 %	No dose adjustment of methadone is necessary of either agent.

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 DALIMUNE in women of childbearing potential to exclude inadvertent (unintentional) use of DALIMUNE during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and 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 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 mothers 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

Patients should be informed that dizziness has been reported during treatment with dolutegravir.

4.8 Undesirable effects

The following side effects have been observed with the use of dolutegravir

System Order Class (SOC)	Frequency	Side Effects
Immune system disorders	*Rare:*	Hypersensitivity; Immune Reconstitution Syndrome (see **section 4.4**)**
Psychiatric disorders	*Frequent:*	Insomnia; abnormal dreams; depression

	Rare:	Suicidal ideation or suicide attempt (particularly in patients with pre-existing history of depression or psychiatric illness)
Nervous system disorders	*More Frequent:*	Headache
	Frequent:	Dizziness
Gastrointestinal disorders	*More Frequent:*	Nausea, diarrhoea
	Frequent	Vomiting; flatulence; upper abdominal pain; abdominal pain; abdominal discomfort
Hepatobiliary disorders	*Rare:*	Hepatitis
Skin and subcutaneous tissue disorders	*Frequent:*	Rash; pruritus
General disorders and administration site conditions	*Frequent:*	Fatigue
Investigations	*Frequent*	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations; Creatinine phosphokinase (CPK) elevations

**See below under Description of selected side effects

Description of selected side effects

Changes in laboratory biochemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. A mean change from baseline of 9,96 µmol/l was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

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 or to Cipla Medpro (Pty) Ltd (by e-mail: drugsafetysa@cipla.com

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 – Antimicrobial (Chemotherapeutic) Medicine. Other than antibiotics. Antiviral Medicine.

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: 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 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 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

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The

PK variability of dolutegravir is low to moderate. In Phase 1 studies in healthy subjects, between-subject CVb % for AUC and C_{max} ranged from ~20 to 40 % and $C\tau$ 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 well absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for the tablet formulation.

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 33 %, 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 may be clinically relevant in the presence of certain integrase class resistance. Therefore, DALUMINE is recommended to be taken with food by patients infected with HIV with integrase class resistance.

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 is 17 L to 20 L in HIV-infected patients, based on population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of concentration. Total blood and plasma medicine-related radioactivity concentration ratios, averaged between 0,441 to 0,535, indicating, minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.

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). Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6-10 % of those in corresponding plasma at steady state. AUC in semen is 7 % and 17 % in rectal tissue of those in corresponding plasma at steady state.

Metabolism

Dolutegravir is primarily metabolised through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance 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 active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two 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) is approximately 1 L/hr in HIV-infected patients based on a population pharmacokinetic analysis.

Linearity/non-linearity

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, 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 to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg once daily.

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 oral dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 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.

Renal impairment

Renal clearance of unchanged active substance 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 mL/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40 % in subjects with severe renal impairment. The mechanism of decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. A single dose of 50 mg of

dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1,5 to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate 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 NR1/2 were not associated with differences in 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

- Colloidal silicon dioxide,
- mannitol,

- microcrystalline cellulose,
- povidone,
- sodium starch glycolate,
- sodium stearyl fumarate.
- Opadry II (Iron oxide red/yellow, macrogol/polyethylene glycol, polyvinyl alcohol-part hydrolysed, talc, titanium dioxide)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep out of reach of children.

6.5 Nature and contents of container

DALIMUNE Tablets are packed in 50 cc white high-density polyethylene (HDPE) bottle with 33 mm child resistant (CRC) cap with heat seal 130-20 liner containing 30 tablets.

7 HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

1474 South Coast Road

Mobeni

Durban

4052

Customer care number: 080 2226662

8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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