SUMMARY OF PRODUCT CHARACTERISTICS

Dolutegravir Tablets 50 mg

1. NAME OF THE MEDICINAL PRODUCT
Dolutegravir Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Dolutegravir Sodium
Equivalent to dolutegravir.....50 mg
Mannitol.....144.400 mg
Sodium.....5.55 mg

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

3. PHARMACEUTICAL FORM
Light brown to brown film coated, capsule shaped tablets debossed with “RL 75” on one side and a break line on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Dolutegravir is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children above 6 years of age.

4.2. Posology and method of administration

Dolutegravir Tablets are available in the strength of 50 mg only and may not be suitable for all dosage recommendations given below. Therefore, other suitable available strengths and/or dosage forms of dolutegravir should be used in such cases.
Dolutegravir should be prescribed by physicians experienced in the management of HIV infection.

Posology
Adults
Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class

The recommended dose of dolutegravir is 50 mg (one tablet) orally once daily.

Dolutegravir should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Please refer to **section 4.5**.

Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)

The recommended dose of dolutegravir is 50 mg (one tablet) twice daily.

In the presence of documented resistance that includes Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I, modelling suggests that an increased dose may be considered for patients with limited treatment options (less than 2 active agents) due to advanced multiclass resistance (see **section 5.2**).

The decision to use dolutegravir for such patients should be informed by the integrase resistancepattern (see **section 5.1**).

Adolescents aged 12 and above

In adolescents (12 to less than 18 years of age and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily. In the presence of integrase inhibitor resistance, there are insufficient reported data to recommend a dose for dolutegravir in adolescents.

Children 6 to less than 12 years of age

In patients infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir in children (6 to less than 12 years of age and weighing at least 15 kg) is determined according to the weight of the child. In the presence of integrase inhibitor resistance,there are insufficient reported data to recommend a dose for dolutegravir in children. Dose recommendations according to weight are presented in Table 1.

Table 1: Paediatric dose recommendations

Body weight (kg)	**Dose**
15 to less than 20	20 mg once daily (Taken as two 10 mg tablets)*
20 to less than 30	25 mg once daily**
30 to less than 40	35 mg once daily (Taken as one 25 mg and one 10 mg tablet)*
40 or greater	50 mg once daily

*Sun Pharmaceutical's Dolutegravir tablets are not suitable for dosage administration in the paediatric weight bands (15 kg to less than 20 kg and 30 kg to less than 40 kg). Other suitable available strengths of dolutegravir from other manufacturers/ suppliers should be used in such paediatric weight bands.
**Score line is functional and is meant to divide the tablet into equal parts to facilitate paediatric dose for the paediatric weight band (20 kg to less than 30 kg).

Missed doses

If the patient misses a dose of dolutegravir, the patient should take dolutegravir as soon as possible, provided the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Elderly

There are limited reported data available on the use of dolutegravir in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see **section 5.2**).

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**).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are reported in patients with severe hepatic impairment (Child-Pugh grade C); therefore dolutegravir should be used with caution in these patients (see **section 5.2**).

Paediatric population

The safety and efficacy of dolutegravir in children aged less than 6 years or weighing less than 15 kg have not yet been established. In the presence of integrase inhibitor resistance, there are insufficient reported data to recommend a dose for dolutegravir in children and adolescents. Currently reported data are described in **section 4.8, and 5.2**, but no recommendation on a posology can be made.

Method of administration

Oral use.

Dolutegravir can be taken with or without food (see **section 5.2**). In the presence of integrase class resistance, dolutegravir should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations) (see **section 5.2**).

The tablets can also be administered by dispersing in ½ cup or approximately 100 ml of water and stirring until a uniform dispersion is obtained

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in **section 6.1**.
- Co-administration with dofetilide (see **section 4.5**).

4.4. Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to preventtransmission should be taken in accordance with national guidelines.

Integrase class resistance of particular concern

The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring Q148+≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I (see **section 5.1**). To what extent dolutegravir provides added efficacy in the presence of such integrase class resistance is uncertain (see **section 5.2**).

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect medicinal products should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or monthsof initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/ or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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

Opportunistic infections

Patients should be advised that dolutegravir or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Drug interactions

Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/ aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain anti-epileptic medicinal products)(see **section 4.5**).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control (see **section 4.5**). Metformin is eliminated renally and, therefore, itis of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, biphosphonates, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Lamivudine and dolutegravir

The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily was explored in two reported large randomized and blinded studies. This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine.

4.5. Interaction with other medicinal products and other forms of interaction

Effect of other agents on the pharmacokinetics of dolutegravir

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

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 2). Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 2).

The absorption of dolutegravir is reduced by certain anti-acid agents (see Table 2).Effect of dolutegravir on the pharmacokinetics of other agents
In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on reported *in vivo* and/or *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (for more information see **section 5.2**).

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was reported in patients.

In vivo, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 or MATE-1 (e.g. dofetilide, metformin) (Table 2 and **section 4.3**).
In vitro, dolutegravir inhibited the renal uptake transporters, organic anion transporters (OAT1) and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied *in vivo*. Dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OAT3.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table 2.

Interaction table

Interactions between dolutegravir and co-administered medicinal products are listed in Table 2 (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "C ").

Table 2: Drug interactions

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% C ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when co- administered with etravirine without boosted protease inhibitors. In paediatric patients the weight-based once daily dose should be administered twice daily. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistantpatients.
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% C ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% C ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.

Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% C ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include efavirenz should be considered (see **section 4.4**).
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as reported with efavirenz is expected, due to induction)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered (see **section 4.4**).
Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% C ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		
Tenofovir	Dolutegravir ↔AUC ↑ 1% C_{max} ↓ 3% C ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% C ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir (see **section 5.2**) due to lack of reported data.
Atazanavir/ ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% C ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir (see **section 5.2**) due to lack of reported data.

Tipranavir/ ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% C ↓ 76% (induction of	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. In paediatric patients the weight- based once daily dose should be administered twice daily. In the presence of integrase class resistance this

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	UGT1A1 and CYP3A enzymes)	combination should be avoided (see **section 4.4**).
Fosamprenavir/ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% C ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence ofintegrase class resistance. In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavirshould be considered.
Nelfinavir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% C_{24} ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔AUC ↓ 4% C_{max} ↔ 0% C_{24} ↓ 6%	No dose adjustment is necessary.
Other Antiviral agents		
Boceprevir	Dolutegravir ↔AUC ↑ 7% C_{max} ↑ 5% C ↑ 8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% C ↑ 45% Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No doseadjustment is necessary.
Other agents		
Antiarrhythmics		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration (see **section 4.3**).
Anticonvulsants		

Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% C ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Oxcarbazepine Phenytoin	Dolutegravir ↓ (Not studied,	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic

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Phenobarbital	decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	inducers. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Azole anti-fungal agents		
Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on reported data from other CYP3A4 inhibitors, a 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 reported with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include St. John's wort should be used where possible in INI-resistant patients.
Antacids and supplements		
Magnesium/ aluminium-containingantacid	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or6 hours before).

Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56% (Complex binding to polyvalent ions)	
Multivitamin	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions)	
Corticosteroids		

Prednisone	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% C ↑ 17%	No dose adjustment is necessary.
Antidiabetics		
Metformin	Metformin ↑ When co-administered with dolutegravir 50mg once daily: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (see **section 4.4**).
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43 % C ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see **section 4.4**).
Rifabutin	Dolutegravir ↔AUC ↓ 5% C_{max} ↑ 16% C ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Oral contraceptives		
Ethinyl estradiol (EE) and Norelgestromin (NGMN)	Dolutegravir ↔EE ↔ AUC ↑ 3% C_{max} ↓ 1 % NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Analgesics		

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

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Paediatric population

Interaction studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of dolutegravir. WOCBP who are taking dolutegravir should use effective contraception throughout treatment.

Pregnancy

Preliminary data from a reported surveillance study has suggested an increased incidence of neural tube defects (0.9%) in mothers exposed to dolutegravir at the time of conception compared with mothers exposed to non-dolutegravir containing regimens (0.1%). The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births (0.05-0.1%). As neural tube defects occur within the first 4 weeks of foetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy. Due to the potential risk of neural tube defects, dolutegravir should not be used during the first trimester unless there is no alternative.

More than 1000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of malformative and foeto/neonatal negative effects. However, as the mechanism by which dolutegravir may interfere in human pregnancy is unknown, the safety in use during the second and third trimester cannot be confirmed. Dolutegravir should only be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the foetus.

In reported animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified (see **section 5.3**). Dolutegravir was reported to cross the placenta in animals.

Breast-feeding

It is unknown whether dolutegravir is excreted in human milk. Available toxicological data in animals has reported excretion of dolutegravir in milk. In lactating rats that received a single oral dose of 50 mg/kg at 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than blood. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

There are no data on the effects of dolutegravir on human male or female fertility. Reported 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 bornein mind when considering the patient's ability to drive or operate machinery.

4.8. Undesirable effects

Summary of the safety profile

The most severe adverse reaction, reported in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see **section 4.4**). The most commonly reported treatment emergent adverse reactions were nausea (13%), diarrhoea (18%) and headache (13%).

Tabulated list of adverse reactions

The adverse reactions considered at least possibly related to dolutegravir are listed by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 3: Adverse reactions

Immune system disorders	Uncommon	Hypersensitivity (see **section 4.4**)
	Uncommon	Immune Reconstitution Syndrome (see **section 4.4**)**
Psychiatric disorders	Common	Insomnia
	Common	Abnormal dreams
	Common	Depression
	Common	Anxiety
	Uncommon	Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing depression or psychiatric illness. history of
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinaldisorders	Very common	Nausea
	Very common	Diarrhoea
	Common	Vomiting
	Common	Flatulence

	Common	Upper abdominal pain
	Common	Abdominal pain
	Common	Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Acute hepatic failure
Skin and subcutaneous tissuedisorders	Common	Rash
	Common	Pruritus
Musculoskeletal and connective tissuedisorders	Uncommon	Arthralgia
	Uncommon	Myalgia
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Alanine aminotransferase (ALT) and/or Aspartateaminotransferase (AST) elevations
	Common	Creatine phosphokinase (CPK) elevations

**see below under Description of selected adverse reactions.

Description of selected adverse reactions

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 reported 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.

Co-infection with Hepatitis B or C

In reported phase III studies patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit ofnormal (ULN). 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 of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see **section 4.4)**.

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see **section 4.4**).

Paediatric population

Based on limited reported data in children and adolescents (6 to less than 18 years of age and weighing at least 15 kg), there were no additional types of adverse reactions beyond those reported in the adult population.

4.9. Overdose

There is currently limited experience with overdosage in dolutegravir.

Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed nospecific symptoms or signs, apart from those listed as adverse reactions.

Further 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

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AX12

Mechanism of Action

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.

Pharmacodynamic effects

Antiviral activity in cell culture

The IC_{50} for dolutegravir in various lab strains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC_{50s} were seen for clinical isolates without any major

difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC_{50} value was 0.2 nM (range 0.02-2.14). The mean IC_{50} for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

Antiviral activity in combination with other antiviral agents
No antagonistic effects *in vitro* were reported with dolutegravir and other antiretrovirals tested: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc and raltegravir. In addition, no antagonistic effects were reported for dolutegravir and adefovir, and ribavirin had no apparent effect on dolutegravir activity.

Effect of human serum
In 100% human serum, the mean protein fold shift was 75 fold, resulting in protein adjusted $IC_{90}$of 0.064 µg/mL.

Resistance

Resistance in vitro

Serial passage is used to study resistance evolution *in vitro*. When using the lab-strain HIV-1 IIIB during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and F, resulting in a maximal fold change in susceptibility of 4 (range 2-4). These mutations were not selected in patients treated with dolutegravir in the reported clinical studies. Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

In further selection experiments using clinical isolates of subtype B, mutation R263K was reported in all five isolates (after 20 weeks and onwards). In subtype C and A/G isolates the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two ART experienced, INI naive individual patients with subtypes B and C in the clinical program, but without effects on dolutegravir susceptibility *in vitro*. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10), but was not detected in patients receiving dolutegravir in the reported phase III program.

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the *in vitro* susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site directed mutants, dolutegravir susceptibility is still unchanged (FC < 2 vs wild type virus), except in the case of Q148-mutations, where a FC of 5-10 or higher is reported with combinations of certain secondary mutations. The effect by the Q148-mutations (H/R/K) was also verified in passage experiments with site directed mutants. In serial passage with strain NL432, starting with site directed mutants harbouring N155H or E92Q, no further selection of resistance was reportrd

(FC unchanged around 1). In contrast, starting with mutants harbouring mutation Q148H (FC 1),a variety of secondary mutations were reported with a consequent increase of FC to values >10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against94% of the 705 clinical isolates.

Resistance in vivo

In previously untreated patients receiving dolutegravir + 2 NRTIs in reported clinical studies, no development of resistance to the integrase class, or to the NRTI class was reported (follow-up of48-96 weeks).

In patients with prior failed therapies, but naïve to the integrase class, integrase inhibitor substitutions were reported in patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected *in vitro* (see above).

In the presence of integrase class-resistance in the following mutations were reportedly selected in patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimized background agents): L74L/M, E92Q, T97A, E138K/A/T, G140S, Y143H, S147G, Q148H/K/R, and N155H and
E157E/Q. Treatment emergent integrase resistance typically reported in patients with a history of the Q148-mutation (baseline or historic). Further subjects experienced PDVF between weeks
24 and 48, which were treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations reported were L74I, N155H.

A reported clinical study examined dolutegravir (plus optimized background therapy) in subjects with primary genotypic resistance to INIs at screening. Treatment-emergent mutations were reported to be consistent with those reported in another clinical study.

<u>Effects on electrocardiogram</u>
No relevant effects were reported on the QTc interval, with doses exceeding the clinical dose by approximately three fold.

5.2. Pharmacokinetics properties

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. In reported phase I studies in healthy subjects, between-subject CVb% for AUC and C_{max} ranged from ~20 to 40% and C 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 reported to be rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for 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, dolutegravir is recommended to be taken with food by patients infected with HIV with integrase class resistance (see **section 4.2**).

The absolute bioavailability of dolutegravir has not been established.Distribution
Dolutegravir is highly bound (>99%) to human plasma proteins based on reported *in vitro* data. The apparent volume of distribution is reported to be 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir 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. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as reported in subjects with moderate hepatic impairment.

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}).

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 was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation

Dolutegravir is primarily metabolized 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 oftotal 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).

Drug interactions

In vitro, dolutegravir 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, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this reported data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see **section 4.5**).

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Elimination
Dolutegravir has a terminal half-life of ~14 hours. The apparent oral clearance (CL/F) isapproximately 1L/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 nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from2 to 100 mg; however increase in dolutegravir exposure appears dose proportional from 25 mg 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.

Pharmacokinetic/pharmacodynamic relationship(s)

In a reported randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy demonstrated rapid and dose-dependent antiviral activity, with mean decline in

HIV-1 RNA of 2.5 log_{10} at day 11 for 50 mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

PK/PD modelling using pooled data from reported clinical studies in integrase resistant patients suggest that increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of dolutegravir in patients with integrase resistance and limited treatment options due to advanced multi class resistance. The proportion of responders (HIV-1 RNA <50 c/mL)at week 24 was predicted to increase around 4-18% in the subjects with Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in reported clinical trials, this high dose may be considered in the presence of the Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with overall limited treatment options due to advanced multi class resistance. There is no reported clinical data on the safety or efficacy of the 100 mg twice daily dose. Co-treatment with atazanavir increases the exposure of dolutegravir markedly, and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.

Special patient populations

Children
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 oral dosage resulted in dolutegravir exposure comparable to that reported in adults who received dolutegravir 50 mg orally once daily. The pharmacokinetics was evaluated in children 6 to 12 years of age and reported that 25 mg once daily in patients weighing at least 20 kg and 35 mg once daily in patients weighing at least 30 kg resulted in dolutegravir exposure comparable to adults. In addition, population PK modelling and simulation analyses showed dosing of dolutegravir tablets on a weight-band basis (20 mg, 25 mg, 35 mg, 50 mg) in children of atleast 6 years of age weighing at least 15 kg provides comparable exposure to that observed in adults (50 mg), with the lowest weight band of 15 to <20 kg corresponding to 20 mg daily.

Elderly

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

Reported pharmacokinetic data for dolutegravir in subjects > 65 years of age are limited.

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was reported 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 for the decrease is unknown. No dosage adjustment is considered necessary forpatients with renal impairment. Dolutegravir has not been studied in patients on dialysis.

Hepatic impairment

Dolutegravir is primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to subjects with moderate hepatic impairment (Child-Pugh class B) and to 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 reported 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 drug metabolising enzymes

There is no evidence that common polymorphisms in drug 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 UGT1A1 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.

Gender

Population PK analyses using pooled pharmacokinetic data from reported adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

Race

Population PK analyses using pooled pharmacokinetic data from reported adult trials revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese subjects appear similar to reported parameters in Western (US) subjects.

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 reported data on subjects with hepatitis B co-infection.

5.3. Preclinical safety data

Dolutegravir was not reported to be mutagenic or clastogenic using *in vitro* tests in bacteria andcultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in reported long term studies in the mouse and rat.

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (24 times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (27times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was reported at 1000 mg/kg (0.40 times the 50 mg twice daily human clinical exposure based on AUC).

In a reported juvenile toxicity study in rats, dolutegravir administration resulted in two pre-weanling deaths at 75 mg/kg/day. Over the pre-weaning treatment period, mean body weight gain was decreased in this group and the decrease persisted throughout the entire study for females during the post-weaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was ~17-20-fold higher than humans at the recommended pediatric exposure. There were no new target organs identified in juveniles compared to adults. In the rat pre/post-natal development study, decreased body weight of the developing offspring was reported during lactation at a maternally toxic dose (approximately 27 times human exposure at the maximum recommended human dose).

The effect of prolonged daily treatment with high doses of dolutegravir has been reported in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeysoccurred at 15 times the human mg/kg equivalent dose (based on a 50 kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, talc, magnesium stearate, Opadry II85F565260, Brown (Polyvinyl alcohol-part hydrolysed, titanium dioxide, macrogol/PEG, talc, Iron oxide yellow and iron oxide red)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 Months

After opening of container tablets should be consumed within 180 days and not later than the expiry date.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.Keep this medicines out of the reach of children.
Store below 30°C.
Product should be stored in the original package.

6.5. Nature and contents of container

HDPE (high density polyethylene) bottles closed with polypropylene screw /child resistant closures.

30's and 90's HDPE bottle Pack. The bottles can be supplied with or without a carton.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Marketing Authorization Holder:
Sun Pharmaceutical Industries Limited
Sun House, 201 B/1, Western Express Highway, Goregaon (East), Mumbai – 400063, India.

8. MARKETING AUTHORISATION NUMBER(S)

TAN 22 HM 0336

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/09/2022

10. DATE OF REVISION OF THE TEXT