

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Dolutegravir 50 mg tablets

2. Qualitative and quantitative composition

Each tablet contains 50 mg of dolutegravir.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

Light orange-coloured, round-shaped, biconvex film-coated tablet debossed with “LA54” on one side and plain 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 and adolescents weighing at least 40 kg.

Consideration should be given to official treatment guidelines for HIV-1 infection, e.g., by WHO. For the use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g., those by WHO, should be consulted.

4.2 Posology and method of administration

Dolutegravir tablets should be prescribed by a healthcare provider experienced in the management of HIV infection.

Posology

Adults

The dose in adults with HIV-1 infection not resistant to integrase inhibitors is dolutegravir 50 mg (one tablet) once daily.

The dose should be 50 mg twice daily if:

- dolutegravir is used with medicines such as efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin (see section 4.5).
- the patient's HIV-1 infection is known or suspected to be resistant to integrase inhibitors.

When HIV-1 genotype testing is available and for patients whose treatment options are limited (fewer than 2 active antiretrovirals) due to advanced multi-class resistance, a higher dose of dolutegravir may be considered. Such resistance may include Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T and L74I.

The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern. In these patients dolutegravir should not be given with some medicines (e.g., efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin); see section 4.5.

Adolescents weighing at least 40kg

The dose in adolescents weighing at least 40 kg with HIV-1 infection not resistant to integrase inhibitors is dolutegravir 50 mg (one tablet) once daily. There is insufficient information on the use of dolutegravir in adolescents with HIV-1 infection resistant to integrase inhibitors.

Children

The dose of dolutegravir for children aged over 6 years is based on the child's body weight (around 1mg/kg). However, other formulations containing lower amounts of dolutegravir are required for children weighing less than 40 kg. There is insufficient information on the use of dolutegravir in children aged less than 6 years.

Elderly

There is insufficient information 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 dose adjustment is needed for patients with renal impairment. The use of dolutegravir has not been studied in patients on dialysis but the dose is not expected to be different for these patients.

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data is available in patients with severe hepatic impairment (Child-Pugh grade C), therefore, dolutegravir should be used with caution in these patients.

Missed dose

If the patient misses a dose of dolutegravir, the patient should take it 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 take the next dose at the usual time.

Method of administration

Oral use.

Dolutegravir can be taken with food or between meals. If HIV-1 is resistant to integrase inhibitors, dolutegravir should preferably be taken with food to increase absorption (particularly in patients with Q148 mutations).

4.3 Contraindications

Hypersensitivity to dolutegravir or any of the excipients listed in section 6.1.
Co-administration with dofetilide.

4.4 Special warnings and precautions for use

General

Effective antiviral therapy can substantially reduce the risk of sexual transmission. However, the risk may not be eliminated. Therefore, to prevent transmission, it is essential to take precautions according to national and other authoritative guidelines.

HIV-1 resistant to integrase inhibitors

The decision to use dolutegravir in the presence of HIV-1 resistance to integrase inhibitors should

take into account that it is considerably less active against viral strains with Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I. Dolutegravir's contribution to efficacy is uncertain when it is used to treat HIV-1 with this type of resistance to integrase inhibitors.

Hypersensitivity Reactions

Hypersensitivity reactions reported with dolutegravir are characterised by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect substances should be discontinued immediately if hypersensitivity reactions develop (including severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, and angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect 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, when starting combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravate symptoms. Typically, such reactions occur within the first few weeks or months of CART. Examples of such conditions are cytomegalovirus retinitis, generalised or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treated when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported in the setting of immune reconstitution but the reported time to onset is more variable and these events can occur many months after starting treatment.

Raised liver enzymes, consistent with immune reconstitution syndrome, occurred in some patients who also had hepatitis B or C infection at the start of dolutegravir therapy. Monitoring of liver function is recommended in patients with hepatitis B or C infection. Particular care should be taken in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in patients with hepatitis B.

Opportunistic infections

Patients receiving dolutegravir/lamivudine/tenofovir disoproxil fumarate or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by healthcare providers experienced in the treatment of HIV infection.

Osteonecrosis

Osteonecrosis has been reported particularly in patients with advanced HIV disease or following long-term combination antiretroviral therapy. Their aetiology can be multifactorial and include corticosteroid use, excessive alcohol consumption, severe immunosuppression, and being overweight. Patients should be advised to speak to their healthcare provider if they have joint aches and pain, joint stiffness or difficulty in movement.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on dolutegravir

Factors that lower the plasma concentration of dolutegravir should be avoided in the presence of HIV-1 resistant to integrase inhibitors. This includes concomitant use of medicines that reduce

blood concentration of dolutegravir (e.g., magnesium- or aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, rifapentine, St. John's wort and certain antiepileptic medicines) (see table, below).

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

Dolutegravir can increase metformin concentrations.

In vivo, dolutegravir did not affect midazolam, a CYP3A4 probe. Based on *in vivo* and *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of major enzymes or transporters such as CYP3A4, CYP2C9 and P-gp (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 in creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 and/or MATE-1 (e.g., fampridine [also known as dalfampridine], metformin).

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 the following table, the pharmacokinetic data reflect studies in adults.

Interaction table

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

Medicines by therapeutic area	Interaction Changes are shown as geometric mean	Recommendations on co-administration
ANTI-INFECTIVES		
Antiretrovirals		
<i>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</i>		
Etravirine without boosted protease inhibitors/	Dolutegravir ↓ AUC ↓ 71%; C _{max} ↓	Etravirine decreased plasma concentration. The dolutegravir

dolutegravir	52%; C _τ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	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 given twice daily. When used with etravirine for infection-resistant to integrase inhibitors, dolutegravir should be co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. (See below in the table).
Lopinavir/ritonavir + etravirine/dolutegravir	Dolutegravir ↔ AUC ↑ 11%; C _{max} ↑ 7%; C _τ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine/dolutegravir	Dolutegravir ↓ AUC ↓ 25%; C _{max} ↓ 12%; C _τ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57%; C _{max} ↓ 39%; C _τ ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with efavirenz. In paediatric patients, the weight-based once-daily dose should be given twice daily. For infection-resistant integrase inhibitors, alternative combinations that do not include efavirenz should be considered.
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with nevirapine. In paediatric patients, the weight-based once-daily dose should be given twice daily. For infection-resistant integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12%; C _{max} ↑ 13%; C _τ ↑ 22%	No dose adjustment is necessary.

	Rilpivirine ↔	
<i>Nucleoside reverse transcriptase inhibitors (NRTI)</i>		
Tenofovir disoproxil	Dolutegravir ↔ AUC ↑ 1%; C _{max} ↓ 3%; C _τ ↑ 8% Tenofovir ↔	No dose adjustment is necessary.
<i>Protease inhibitors (PIs)</i>		
Atazanavir	Dolutegravir ↑ AUC ↑ 91%; C _{max} ↑ 50%; C _τ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Atazanavir+ritonavir/	Dolutegravir ↑ AUC ↑ 62%; C _{max} ↑ 34%; C _τ ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Tipranavir + ritonavir/ dolutegravir	Dolutegravir ↓ AUC ↓ 59%; C _{max} ↓ 47%; C _τ ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with tipranavir/ritonavir. In paediatric patients, the weight-based once-daily dose should be given twice daily. In the presence of integrase class resistance, this combination should be avoided.
Fosamprenavir/ritonavir	Dolutegravir ↓ AUC ↓ 35%; C _{max} ↓ 24%; C _τ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. For infection-resistant integrase inhibitors, alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22%; C _{max} ↓ 11%; C _{24hours} ↓ 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.
<i>Antivirals against hepatitis C</i>		
Boceprevir	Dolutegravir ↔ AUC ↑ 7%; C _{max} ↑ 5%; C _τ ↑ 8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Daclatasvir ↔ Dolutegravir ↔ AUC ↑ 33%; C _{max} ↑ 29%; C _τ ↑ 45%	No dose adjustment is necessary.
Elbasvir/grazoprevir Glecaprevir/pibrentasvir Ledipasvir/sofosbuvir Ombitasvir/paritaprevir Ombitasvir/paritaprevir/ dasabuvir Simeprevir Sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/ voxilaprevir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.
Telaprevir	Dolutegravir ↑ AUC ↑ 25%; C _{max} ↑ 19%; C _τ ↑ 37% Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)	No dose adjustment is necessary.
<i>Antibiotics</i>		
Rifampicin	Dolutegravir ↓ AUC ↓ 54%; C _{max} ↓ 43%; C _τ ↓ 72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with rifampicin. In paediatric patients, the weight-based once-daily dose should be given twice daily. For infection resistant to integrase inhibitors, co-administration of dolutegravir and rifampicin should be avoided.
Rifabutin	Dolutegravir ↔ AUC ↓ 5%; C _{max} ↑ 16%; C _τ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
<i>Antifungals</i>		

Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
<i>Antiepileptics</i>		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49%; C _{max} ↓ 33%; C _τ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when given with carbamazepine. In paediatric patients, the weight-based once-daily dose should be given twice daily. Alternatives to carbamazepine should be used in patients with infections resistant to integrase inhibitors.
Oxcarbazepine/ Phenytoin/ Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with these enzyme inducers. In paediatric patients, the weight-based once-daily dose should be given twice daily. Alternatives to these medicines that are not enzyme inducers should be used in patients with infections resistant to integrase inhibitors.
<i>Antiarrhythmics</i>		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potentially life-threatening toxicity caused by high dofetilide concentration.
<i>Antacids and supplements</i>		
Magnesium- or aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74%; C _{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium- or aluminium-containing antacids should be taken well separated in time from dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39%; C _{max} ↓ 37%; C _{24hours} ↓ 39% (Complex binding	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours

	to polyvalent ions)	after or 6 hours before).
Iron supplements	Dolutegravir ↓ AUC ↓ 54%; C _{max} ↓ 57%; C _{24hours} ↓ 56% (Complex binding to polyvalent ions)	
Multivitamins	Dolutegravir ↓ AUC ↓ 33%; C _{max} ↓ 35% C _{24hours} ↓ 32% (Complex binding to polyvalent ions)	
<i>Antidiabetics</i>		
Metformin	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; C _{max} ↑ 66% Co-administered with dolutegravir 50 mg twice daily: Metformin ↑ AUC ↑ 145%; C _{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment, a dose adjustment of metformin should be considered when given with dolutegravir because the risk of lactic acidosis is increased in patients with moderate renal impairment due to increased metformin concentration.
<i>Contraceptives</i>		
Ethinylestradiol and norelgestromin	Dolutegravir ↔ Ethinylestradiol ↔ AUC ↑ 3%; C _{max} ↓ 1% Norelgestromin ↔ AUC ↓ 2%; C _{max} ↓ 11%	Dolutegravir had no pharmacodynamic effect on luteinizing hormone, follicle-stimulating hormone and progesterone. No dose adjustment of oral contraceptives is necessary when given with dolutegravir.
<i>Corticosteroids</i>		
Prednisone	Dolutegravir ↔ AUC ↑ 11%; C _{max} ↑ 6%; C _τ ↑ 17%	No dose adjustment is necessary.
<i>Drug abuse</i>		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2%; C _{max} ↔ 0%; C _τ ↓ 1%	No dose adjustment is necessary.

<i>Herbal products</i>		
St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with St. John's wort. In paediatric patients, the weight-based once-daily dose should be given twice daily. Alternatives to St. John's wort should be used in patients with infection resistant to integrase inhibitors.

4.6 Fertility, pregnancy and breastfeeding

Human and animal data

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

Preliminary data from a surveillance study in Botswana suggested an increased incidence of neural tube defects (NTD) (0.67%) in mothers exposed to dolutegravir at the time of conception compared with mothers exposed to non-dolutegravir containing regimens (0.1%). However, a review of more mature data from the study, along with data from other countries, and modelling of population-level risks and benefits of dolutegravir use in women of childbearing potential, has indicated that the risk of NTD is smaller than initially reported, with a weighted estimated risk of 0.36% (95% CI 0.01 – 0.62). Although the risk of NTD remains statistically higher than the rate with other antiretrovirals and the background rate, the absolute risk is still very low. Continued surveillance is needed to more definitively confirm or refute the neural tube defect signal, and several studies are ongoing to address this. It should be noted that Botswana has no national food folate fortification programme and that most reports on NTDs come from countries where such programmes are in place, which significantly lowers the prevalence of NTDs in the general population.

Neural tube defects occur within the first 4 weeks of foetal development (after which the neural tubes close). The data therefore suggest that any increased risk would be associated with exposure to dolutegravir in the periconception period rather than later in the pregnancy. The same observational study shows that the dolutegravir- and the efavirenz-containing (comparator) antiretroviral regimen when started later in pregnancy have comparable pregnancy outcomes. Dolutegravir has been shown to cross the placenta in animals. In animal reproductive toxicology studies, no adverse development outcomes, including neural tube defects, were identified (see section 5.3).

To better understand what risk there may be, active research and surveillance are ongoing in further pregnant women exposed to dolutegravir at the time of conception.

Women of childbearing potential

Although the absolute risk is low, there remains the possibility of an approximately 3-fold increased risk of neural tube defects in women receiving dolutegravir in the periconception period

compared with other HIV drugs, including efavirenz. Women should be provided with information about benefits and risks, to make an informed choice regarding the use of dolutegravir or other antiretroviral therapy. Preferred alternative options may vary depending on the individual benefit/risk evaluation and local circumstances.

If feasible, women of childbearing potential should undergo pregnancy testing before initiation of dolutegravir.

Pregnancy

Women in the first trimester of pregnancy should be informed about the potential risk of an increased incidence of neural tube defects with the use of dolutegravir. Preferred antiretroviral options may vary depending on the individual benefit/risk evaluation and local circumstances. More than 1,000 outcomes from second and third-trimester exposure in pregnant women indicate no evidence of increased risk of malformations.

Breastfeeding

It is not known if dolutegravir passes into human milk. Animal studies show that dolutegravir appears in milk. In rats receiving a single oral dose of 50 mg/kg 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than in blood. Current recommendations on HIV and breastfeeding (e.g., those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility

There are no data on dolutegravir's effects on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility.

4.7 Effects on the ability to drive and use machines

Patients should be informed that dolutegravir can cause dizziness. The patient's clinical status and side effects of dolutegravir should be considered for evaluating the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Data from clinical trials were used to estimate the frequency of adverse events linked to dolutegravir treatment. The most severe adverse reactions are hypersensitivity reactions that include rash and severe liver effects. The most common adverse reactions of dolutegravir are nausea (13%), diarrhoea (18%) and headache (13%).

The adverse reactions considered related to dolutegravir are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common ($\geq 1/10$), common (1/100 to 1/10), uncommon (1/1000 to 1/100), rare (1/10 000 to 1/1000), and very rare ($< 1/10\ 000$).

Immune system disorders	Uncommon	Hypersensitivity (see section 4.4)
		Immune Reconstitution Syndrome (see section 4.4 and also described below)
Psychiatric disorders	Common	Insomnia
		Abnormal dreams
		Depression, anxiety
	Uncommon	Suicidal ideation or suicide attempt (particularly in patients with a history of depression or psychiatric illness)

Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Very common	Nausea
		Diarrhoea
	Common	Vomiting
		Flatulence
		Upper abdominal pain
		Abdominal pain
		Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash
		Pruritus
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia
		Myalgia
General disorders	Common	Fatigue
Investigations	Common	Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) raised creatine kinase

Description of selected adverse reactions

Changes in serum creatinine

Serum creatinine can increase in the first week of treatment with dolutegravir and then remain stable. A mean change from baseline of 10 µmol/L occurred after 48 weeks of treatment. Creatinine increases were comparable between various background regimens. These changes are not considered clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with hepatitis B or C

In clinical studies with dolutegravir, the side effects profile in patients also infected with hepatitis B or C or both was similar to that in patients without hepatitis, provided that the baseline liver function tests did not exceed 5 times the upper limit of normal. However, the rates of AST and ALT abnormalities were higher in patients with hepatitis B or C co-infection. Liver enzyme elevations consistent with immune reactivation syndrome occurred in some subjects with hepatitis B or C co-infection at the start of dolutegravir therapy, particularly in those whose hepatitis B therapy was stopped.

Immune reactivation syndrome

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

Children

The limited data available for children and adolescents (aged 6 to 18 years and weighing at least 15 kg) suggest no additional adverse reactions beyond those that occur in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications

(https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose

Experience of dolutegravir overdosage is limited. Single doses of up to 250 mg in healthy subjects revealed no specific symptoms or signs, apart from those listed as adverse reactions.

There is no specific treatment for dolutegravir overdose. In an overdose, the patient should be treated supportively with appropriate monitoring, as necessary and with advice from a national poisons centre, where available. Dialysis is unlikely to remove dolutegravir to any significant extent because it is highly bound to plasma proteins.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 7.13 Antivirals.

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 IC₅₀ for dolutegravir in various HIV-1 lab strains using peripheral blood mononuclear cells (PBMC) was 0.5 nM, and when using MT-4 cells it ranged from 0.7 to 2 nM. The IC₅₀ was similar for clinical isolates without any major difference between subtypes (A, B, C, D, E, F and G). The mean IC₅₀ for three HIV-2 isolates was 0.18 nM (range 0.09–0.61 nM).

Antiviral activity in combination with other antiviral agents

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

Resistance in vitro

Using strain NL432, mutations E92Q (fold change, FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

Using clinical isolates of subtypes B, C and A/G the integrase substitution R263K and G118R (in C and A/G) R263K was reported from two ART-experienced, integrase-inhibitor-naïve 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 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 an FC is 5–10 or higher with combinations of certain secondary mutations. The effect of 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, further selection of resistance did not occur (FC unchanged around 1). In contrast, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen 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.

In an analysis for susceptibility to dolutegravir in raltegravir-resistant isolates from raltegravir-experienced patients, dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Resistance in vivo (dolutegravir)

In previously untreated patients receiving dolutegravir + 2 NRTIs in clinical studies, resistance did not develop to the integrase inhibitor class or the NRTI class (n=1118 follow-up of 48–96 weeks).

In patients whose previous antiretroviral treatment had failed and who had not received an integrase inhibitor, integrase inhibitor substitutions occurred in 4/354 patients (follow-up 48 weeks) treated with dolutegravir given with an investigator-selected background regimen. Of these four patients, two had a unique R263K integrase substitution, with a maximum FC of 1.93, one had a polymorphic V151V/I integrase substitution, with a maximum FC of 0.92, and one had existing integrase mutations and is assumed to have been integrase-inhibitor-experienced or infected with integrase-inhibitor-resistant virus. The R263K mutation was also selected *in vitro* (see above).

In the presence of integrase-inhibitor class resistance the following mutations were selected after 24 weeks in 32 patients with protocol-defined virological failure (PDVF) and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimised background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and E157E/Q (n=1). Treatment-emergent integrase-inhibitor-resistance typically appeared in patients with a history of the Q148 mutation (baseline or historic). Five further subjects had PDVF between weeks 24 and 48, and 2 of these 5 had treatment-emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1) and N155H (n=2).

Treatment-emergent mutations in 30 subjects with primary genotypic resistance to integrase inhibitors at screening who were treated with dolutegravir (plus optimised background therapy) were consistent with these findings.

Effects on electrocardiogram (dolutegravir)

No relevant effects were seen on the QTc interval, with doses 3-fold higher than the clinical dose.

Clinical efficacy and safety

Previously untreated patients

The efficacy of dolutegravir is based on the analyses of 96-week data from two randomised, international, double-blind, active-controlled trials. This is supported by 96-week data from an open-label, randomised and active-controlled study and additional data from the open-label phase of one study to 144 weeks. Throughout the treatment in these studies, no cases of treatment-emergent primary resistance to the integrase inhibitors or to nucleoside reverse transcriptase occurred in patients treated with dolutegravir.

In therapy-naïve adult patients with HIV infection who received dolutegravir 50 mg once daily with either abacavir/lamivudine or tenofovir disoproxil/emtricitabine, viral load (HIV-1 RNA) was reduced to fewer than 50 copies/ml in 80% of patients after 96 weeks of treatment and was 71% in one study after 144 weeks. Viral suppression was similar to or greater than in the comparator groups.

Patients treated previously with regimens that excluded integrase inhibitors.

One study involved 719 adult patients with HIV-1 who had previously received antiretroviral therapy. Patients received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with an investigator-selected background regimen consisting of up to 2 antiretrovirals. After 48 weeks, viral load was reduced to fewer than 50 copies/ml in 71% of patients receiving a combination containing dolutegravir compared to 64% of patients receiving a combination containing raltegravir.

Patients in whom an integrase inhibitor had failed (patients with HIV-1 resistant to integrase inhibitors) One study involved 183 adult patients with HIV-1 whose antiretroviral treatment had failed and whose infection had developed resistance against raltegravir or elvitegravir or both. After 48 weeks of treatment with dolutegravir 50 mg twice daily and optimised background therapy, the viral load was fewer than 50 copies/ml in 63% of patients. Efficacy was lower in patients with Q148 mutation, particularly when accompanied by two or more secondary mutations.

Another study involved 30 adult patients who had HIV-1 infection with primary genotypic resistance to integrase inhibitors. Patients received either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days. The primary endpoint at day 8 showed that dolutegravir 50 mg twice daily was superior to placebo, with an adjusted mean treatment difference for the change from baseline in plasma HIV-1 RNA of -1.2 log₁₀ copies/mL. After subsequent treatment of all patients with dolutegravir 50 mg twice daily and optimised background therapy, 40% of patients had fewer than 50 copies/mL at week 48.

Paediatric population

A study in children and adolescents aged up to 18 years investigated the pharmacokinetics, tolerability and efficacy of dolutegravir given in a dose of around 1 mg/kg daily in combination

with other antiretrovirals. Patients were divided into two cohorts, each with 23 patients; the first cohort included adolescents aged from 12 to 18 years and the second cohort included patients aged from 6 years to 12 years. The viral load after 24 weeks was fewer than 50 copies/ml in 70% of patients in the first cohort and 61% in the second cohort.

5.2 Pharmacokinetic properties

The absorption characteristics of dolutegravir 50 mg tablets have been determined after administration of a single dose tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value (\pm standard deviation)
Maximum concentration (C_{\max})	2994 \pm 850 ng/mL (2872)
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	55008 \pm 20285 ng·h/mL (51544)
Characteristic	Median (range)
Time to attain maximum concentration (T_{\max})	2.33 (0.67 – 9.00) h

Pharmacokinetics of dolutegravir

General	PK is similar for healthy and HIV-infected subjects. Low to moderate PK variability.
Absorption	
Absolute bioavailability	Not known
Oral bioavailability	At least 32 %

Food effect		AUC (0-∞)	C _{max}	T _{max}
	Low fat	33% ↑	46%	3 h
	Moderate fat	41% ↑	52% ↑	4 h
	High fat	66% ↑	67% ↑	5h
	Increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, it is recommended that patients infected with HIV resistant to integrase inhibitors take dolutegravir with food.			
Distribution				
Volume of distribution (mean)	17 to 20 L			
Plasma protein binding <i>in vitro</i>	>99%, increase in unbound fraction with low serum albumin (as in moderate hepatic impairment)			
Tissue distribution	CSF: mean 18 ng/mL (comparable to unbound plasma concentration, and >IC50) Vaginal, cervical tissue, cervicovaginal fluid: 6-10% Semen: 7% Rectal tissue: 17% (each of the corresponding plasma levels at steady state)			
Metabolism				
	Hepatic metabolism: glucuronidation via UGT1A1 minor pathway CYP3A			
Active metabolite(s)	NA			
Elimination				
Elimination half-life	14 h			
Mean systemic clearance (Cl/F)	≈1 L/h			
% of the dose excreted in urine	32% in total; <1% unchanged, 19% as ether glucuronide Other metabolites; N-dealkylation metabolite and metabolite formed by oxidation at the benzylic carbon			
% of dose excreted in faeces	53% is excreted unchanged in the faeces			
Pharmacokinetic linearity	Depending on dose and formulation. For tablets: Dose-proportional increases from 25 to 50 mg			
Drug interactions (<i>in vitro</i>)				
Transporters	No relevant inhibition of P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. No substrate of human OATP 1B1, OATP 1B3 or OCT 1.			
Metabolizing enzymes	No relevant inhibition of (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19,			

	CYP2D6 CYP3A, uridine diphosphate glucuronosyltransferase (UGT)1A1 or UGT2B7. No induction of CYP1A2, CYP2B6 or CYP3A4.
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Pharmacokinetic/pharmacodynamic relationship

A dose-ranging trial involving dolutegravir monotherapy found rapid and dose-dependent antiviral activity, with a mean decline in HIV-1 RNA of 2.5 log₁₀ at day 11 for a 50-mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Modelling of pooled data from clinical studies in integrase-inhibitor-resistant patients suggests that increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of dolutegravir in patients with integrase-inhibitor-resistance and limited treatment options due to advanced multi-class resistance. The proportion of responders (HIV-1 RNA < 50 copies/mL) at week 24 was predicted to increase around 4–18% in the subjects with Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in clinical trials, this high dose may be considered in the presence of the Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with limited treatment options due to advanced multi-class resistance. There are no 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 populations

Children

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 up to 18 years of age) found that a dose of dolutegravir 50 mg once daily resulted in dolutegravir exposure comparable to that in adults who received a dose of 50 mg once daily. The pharmacokinetics in 11 children aged 6 to 12 years found 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 on a weight-band basis (20, 25, 35, and 50 mg) in children of at least 6 years of age weighing at least 15 kg provides comparable exposure to those in adults (50 mg), with the lowest weight band of 15–20 kg corresponding to 20 mg 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 aged over 65 years is limited.

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. Pharmacokinetics of 50-mg dolutegravir was studied in adults with severe renal impairment (creatinine clearance less than 30 ml/minute) and matched healthy controls. The exposure to dolutegravir was decreased by about 40% in subjects with severe renal impairment. The mechanism for the 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. When a single dose of dolutegravir 50 mg was given to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and 8 matched healthy adult controls, the total dolutegravir concentration in plasma was similar. However, there was a 1.5- to 2-fold increase in unbound dolutegravir in 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

Common polymorphisms in drug metabolising enzymes have not been found to alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics, subjects with UGT1A1 genotypes had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1.

Co-infection with hepatitis B or C

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

Gender

Analyses of pooled pharmacokinetic data from trials in adults revealed no clinically relevant effect of gender on the exposure to dolutegravir.

Race/ethnicity

Population PK analyses using pooled pharmacokinetic data from trials in adults revealed no clinically relevant effect of race on the exposure of dolutegravir.

5.3 Preclinical safety data

Dolutegravir

Dolutegravir was not mutagenic or clastogenic in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long-term studies in mice and rats.

Dolutegravir did not affect male or female fertility in rats at doses up to 24 times the 50 mg twice daily human clinical exposure based on AUC. Oral administration of dolutegravir to pregnant rats at doses up to 27 times the 50 mg twice daily human clinical exposure based on AUC from days 6 to 17 of gestation did not cause maternal toxicity, developmental toxicity or teratogenicity.

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. In rabbits, maternal toxicity (decreased food consumption, reduced urine or faeces, suppressed body weight gain) was observed at 1000 mg/kg.

In a juvenile toxicity study in rats, there were two pre-weanling deaths at a dolutegravir dose of 75 mg/kg daily. Over the pre-weaning period, mean bodyweight gain was decreased and the decrease persisted throughout the study for females during the post-weaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was about 17 to 20-fold higher than in humans at the recommended paediatric exposure. No new target organs were identified in juveniles compared to adults. In the rat, prenatal and postnatal development study, body weight decreased in the

developing offspring during lactation at a maternally toxic dose (about 27 times human exposure at the maximum recommended dose).

The primary effect of high doses of dolutegravir and prolonged daily treatment (up to 26 weeks in rats and up to 38 weeks in monkeys) was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures about 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal intolerance is considered to be due to local effects of the active substance, comparison based on body weight or body surface area is appropriate for this toxicity. Gastrointestinal intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50-kg human), and 5 times the human mg/m² equivalent dose for a clinical dose of 50 mg twice daily.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Mannitol

Microcrystalline cellulose

Sodium starch glycolate

Povidone

Sodium starch glycolate

Croscarmellose sodium

Sodium stearyl fumarate

Film coat

Opadry II Orange 85F530143

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of the container

30's Count: The tablets are packed in a white, opaque, 60 cc HDPE bottle closed with a 38 mm child-resistant closure.

90's Count: The tablets are packed in a white, opaque, 85 cc HDPE bottle closed with a 53 mm child-resistant closure.

Pack sizes: 30 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. APPLICANT

Laurus Labs Limited
2nd Floor, Serene Chambers
Road No.-7 Banjara Hills
Hyderabad – 500034
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8. MANUFACTURER

Laurus Labs Limited
Plot No:19, 20 & 21, western sector, APSEZ
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9. REGISTRATION DETAILS

Zimbabwe registration number: 2019/7.13/5923
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF THE TEXT

September 2023