SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir Tablets 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Dolutegravir sodium equivalent to 50 mg of Dolutegravir
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light orange colored, round shaped, biconvex film coated tablets debossed with “LA54” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dolutegravir tablets are indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents weighing at least 40 kg.

Consideration should be given to official treatment guidelines for HIV-1 infection, e.g. by WHO.

For 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 health care 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 fromG140A/C/S, E138A/K/T, 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 bodyweight (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 are 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 the HIV-1 is resistant to integrase inhibitors, dolutegravir should preferably be taken with food to increase absorption (particularly in patients withQ148 mutations).

4.3 Contraindications

Hypersensitivity to dolutegravir or to any of the excipients listed in section 6.1.

Co-administration with dofetilide.

4.4 Special warnings and precautions for use

Effective antiviral therapy can substantially reduce the risk of sexual transmission. However, the riskmay not be eliminated entirely. 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 andcause serious clinical conditions or aggravate symptoms. Typically, such reactions occur within the first fewweeks 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) 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 should be advised that antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications 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 health care provider if they have joint aches and pain, joint stiffness or difficulty in movement.

Excipients

Tablet core
Mannitol, microcrystalline cellulose, sodium starch glycolate, povidone K30 and sodium stearyl fumarate.

Film-coating
Polyvinyl alcohol, titanium dioxide, macrogol, talc, FD&C yellow #6/sunset yellow FCF aluminum lake.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on dolutegravir

Factors that lower 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, 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 enzymesmay 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).

Effects of dolutegravir on other agents

Dolutegravir can increase metformin concentrations.

In vivo, dolutegravir did not have an effect on 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 1 (MATE-1). In patients, creatinine clearance decreased by 10–14% (secretory fraction is dependent on OCT2 and MATE-1 transport). Dolutegravir may increase plasma concentrations of medicines whose excretion involves OCT2 or MATE-1 (e.g. dofetilide, metformin) (see table, below).

In vitro, dolutegravir inhibited the renal uptake transporters, organic anion transporters OAT1 andOAT3. However, based on the lack of effect in vivo on the pharmacokinetics of the OAT substratetenofovir, inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied in vivo. Dolutegravir may increase plasma concentrations of medicines whose excretion is dependent upon OAT3.
Established and theoretical interactions with selected antiretrovirals and non-antiretroviralmedicinal 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 ↔, area under the concentration versus time curve as AUC, maximum observed concentration as Cmax, concentration at end of dosing interval as Cτ).

Drug Interactions

Medicines by therapeutic areas	**Interaction changes shown as geometric mean**	**Recommendations on co-administration**
Antimicrobials		
Antiretroviral		
Non-nucleoside Reverse Transcriptase Inhibitors		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 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-resistant patients (see further below in table).
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75%	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.

	Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	For infection resistant to 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 to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% $C\tau$ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors (NRTI)		
Tenofovir disoproxil	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% $C\tau$ ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors (PIs)		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% $C\tau$ ↑ 180% Atazanavir ↔ (historical controls) (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.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% $C\tau$ ↑ 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 ↓ AUC ↓ 59% C_{max} ↓ 47% $C\tau$ ↓ 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. For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Fosamprenavir/ ritonavir	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% $C\tau$ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. For infection resistant to integrase inhibitors, alternative combinations that do not include fosamprenavir/ritonavir should be considered.

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.
Antivirals against hepatitis C		
Boceprevir	Dolutegravir ↔ AUC ↑ 7% C_{max} ↑ 5% Cτ ↑ 8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	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%; Cmax ↑ 19%; Cτ ↑ 37% Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Antibiotics		
Rifampicin	Dolutegravir ↓ AUC ↓ 54%; Cmax ↓ 43%; Cτ ↓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%; Cmax ↑ 16%; Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Antifungals		

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.
Antiepileptics		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49%; Cmax ↓ 33%; Cτ ↓ 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 infection 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 infection resistant to integrase inhibitors.
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.
Antacids and supplements		
Magnesium- or aluminium-containing antacid	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 or 6 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)	

Antidiabetics		
Metformin	Co-administered with dolutegravir 50mg twice daily: Metformin ↑ AUC ↑ 79% C_{max} ↑ 66% 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 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 givenwith dolutegravir, because the risk of lactic acidosis is increased in patients with moderate renal impairment due to increased metformin concentration.
Contraceptives		
Ethinyl estradiol and Norelgestromin	Dolutegravir ↔ Ethinyl estradiol ↔ 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.
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11%; Cmax ↑ 6%; Cτ ↑ 17%	No dose adjustment is necessary.
Drug abuse		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2%; Cmax ↔ 0%; Cτ ↓ 1%	No dose adjustment is necessary.
Herbal products		
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'swort. 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 withmothers exposed to non-dolutegravir containing regimens (0.1%). However, review of more

mature data fromthe 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.

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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. Preferredalternative 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 use of dolutegravir. Preferred antiretroviral options may vary depending on the individual benefit/risk evaluation and local circumstances.

More than 1000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of malformations.

Breast-feeding

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 breast-feeding (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 indicateno effects of dolutegravir on male or female fertility.

4.7 Effects on ability to drive and use machines

Patients should be informed that dolutegravir can cause dizziness. The patient's clinical status and dolutegravir's side effects should be considered for evaluating the patient's ability to drive oroperate 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 (≥ 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/litre occurred after 48 weeks of treatment. Creatinine increaseswere 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 orC
In clinical studies, 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 enzymes 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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

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 ishighly bound to plasma proteins.

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 IC50 for dolutegravir in various lab-strains using PBMC was 0.5 nM, and when using MT-4 cellsit ranged from 0.7 to 2 nM. The IC50 was similar 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 IC50was 0.2 nM (range 0.02–2.14 nM). The mean IC50 for three HIV-2 isolates was 0.18 nM (range 0.09–0.61nM).

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 subtype 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-naive 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 a FC is 5–10 or higher 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, 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 mutationswere 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 fromraltegravir-experienced patients, dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Resistance in vivo

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

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) treatedwith dolutegravir given with an investigator-selected background regimen. Of these four

patients, two hada unique R263K integrase substitution, with a maximum FC of 1.93, one had a polymorphicV151V/I integrase substitution, with 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. TheR263K mutation was also selected in vitro (see above).

In the presence of integrase-inhibitor class-resistance the following mutations were selected after 24weeks in 32 patients with protocol-defined virological failure (PDVF) and with paired genotypes (all treatedwith 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), 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

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 144weeks. Viral suppression was similar or greater than in the comparator groups.

Patients treated previously with regimens that excluded integrase inhibitor

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 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% 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 oftreatment 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, particularlywhen 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 dailywas superior to placebo, with an adjusted mean treatment difference for the change from baseline in plasmaHIV- 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.

Paediatricpopulation

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

Absorption of Dolutegravir tablets

The absorption characteristics of Dolutegravir tablets have been determined in healthy volunteers as follows:

Characteristic	Arithmetic mean ± Standard deviation (Geometric mean)
Maximum concentration (Cmax)	2994 ± 850 ng/mL (2872)
Area under the curve (AUC0-∞), a measure of the extent of absorption	55008 ± 20285 ng·h/mL (51544)
Characteristic	Median(range)
Time to attain maximum concentration (Tmax)	2.33 (0.67 – 9.00) h

Pharmacokinetics of dolutegravir

	Dolutegravir
General	
	PK similar for healthy and HIV-infected subjects. Low to moderate PK variability
Absorption	
Absolute bioavailability	Not known
Oral bioavailability	At least 32%
Food effect	<table><tr><th></th><th>AUC(0-∞)</th><th>Cmax</th><th>Tmax</th></tr><tr><td>Low fat</td><td>33%</td><td>46%</td><td>3 h</td></tr><tr><td>Moderate Fat:</td><td>41%</td><td>52%</td><td>4 h</td></tr><tr><td>High fat:</td><td>66%</td><td>67%</td><td>5 h</td></tr></table> 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 in vitro	>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 corresponding plasma levels at steady state)
Metabolism	
	Hepatic metabolism: glucuronidation via UGT1A1 minor pathway CYP3A
Active metabolite(s)	N/A
Elimination	14 h
Mean systemic clearance (Cl/F)	1 L/h
% of 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 (invitro)	
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 glucuronosyl

	transferase (UGT)1A1 or UGT2B7 No induction of CYP1A2, CYP2B6 or CYP3A4

Pharmacokinetic/pharmacodynamic relationship

A dose-ranging trial involving dolutegravir monotherapy found rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 log10 at day 11 for 50-mg dose. This antiviral responsewas 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 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-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 fromG140A/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 are limited.

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. Pharmacokinetics of dolutegravir were 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 50mg was given to 8 subjects with moderate hepatic impairment (Child-Pugh class B)

and to 8 matched healthy adult controls, the total dolutegravir concentration in plasma was similar. However, there was a 1.5- to2-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.

Gender

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

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

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.

5.3 Preclinical safety data
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 the mouse and rat.
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 bodyweight gain) was observed at 1000mg/kg.

In a juvenile toxicity study in rats, there were two pre-weanling deaths at dolutegravir dose of 75mg/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, bodyweight 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 bodyweight or on 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 K30 and sodium stearyl fumarate.

Film-coating
Polyvinyl alcohol, titanium dioxide, macrogol, talc, FD&C yellow #6/sunset yellow FCF aluminum lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

30's Count: White opaque 60 cc HDPE bottles closed with 33 mm child resistant closures.

90's Count: White opaque 85 cc HDPE bottles closed with 33 mm child resistant closures.

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. MARKETING AUTHORISATION HOLDER

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India

8. MARKETING AUTHORISATION NUMBER(S)

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