Dolutegravir 50 mg Film-Coated Tablet 75095074

75095074 Dolutegravir 50 mg Film-Coated Tablet

Dolutegravir

50 mg Film-Coated Tablet

Rx

Direct Acting Antiviral

1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir Film-Coated Tablet 50mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains dolutegravir sodium equivalent to 50mg dolutegravir.
Each film-coated tablet contains 145.4 mg of mannitol and 5.2 mg (0.2mmol) of sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dolutegravir (as sodium) 50mg Tabletsis indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20 kg.

Consideration should be given to the most recent official treatment guidelines for HIV-1 infection, e.g. those issued 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 (as sodium) 50mg 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 from G140A/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.

Children and adolescents

The dose in children and adolescents weighing at least 20 kg and with HIV-1 infection not resistant to integrase inhibitors is 50 mg dolutegravir (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). There is insufficient information on the use of dolutegravir in children and adolescents with HIV-1 infection resistant to integrase inhibitors.

For patients weighing less than 20 kg appropriate dose adjustments are not possible with this product.

It should be checked whether other formulations are available.

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 with Q148 mutations).

4.3 Contraindications

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

Dolutegravir must not be administered concurrently with medicines with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including dofetilide and fampridine (also known as dalfampridine; see section 4.5).

4.4 Special warnings and precautions for use

Effective antiviral therapy can substantially reduce the risk of sexual transmission. However, the risk may 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

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) 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. Patients should therefore remain under close clinical observation by health care providers experienced in the treatment of these associated HIV diseases.

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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment.

For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Excipients

Each film-coated tablet contains mannitol, which may have a mild laxative effect.

Each tablet also contains 5.2 mg (0.2 mmol) of sodium, which is less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on dolutegravir

Medicines that lower plasma concentration of dolutegravir should be avoided in the presence of HIV-1 resistant to integrase inhibitors. These medicines include: 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 enzymes may decrease dolutegravir plasma concentration and reduce its therapeutic effect (see table, below). Coadministration 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).

Interaction table

Interactions between dolutegravir and co-administered medicinal products are listed in the following table.

The pharmacokinetic data reflect studies in adults (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).

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Antimicrobials		
Antiretrovirals		
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71%; Cmax ↓ 52%; Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when coadministered 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, or darunavir/ritonavir, or lopinavir/ritonavir (see below in table).
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11%; Cmax ↑ 7%; Cτ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25%; Cmax ↓ 12%; Cτ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57%; Cmax ↓ 39%; Cτ ↓ 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 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%; Cmax ↑ 13%; Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTI)		
Tenofovir disoproxil	Dolutegravir ↔ AUC ↑ 1%; Cmax ↓ 3%; Cτ ↓8% Tenofovir ↔	No dose adjustment is necessary.
Protease inhibitors (PIs)		
Atazanavir	Dolutegravir ↑ AUC ↑ 91%; Cmax ↑ 50%; Cτ ↑ 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%; Cmax ↑ 34%; Cτ ↑ 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%; Cmax ↓ 47%; Cτ ↓ 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%; Cmax ↓ 24%; Cτ ↓ 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%; Cmax ↓ 11%; C24hours ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4%; Cmax ↔ 0%; C24hours ↓ 6%	No dose adjustment is necessary.
Antivirals against hepatitis C		
Daclatasvir	Dolutegravir ↔ AUC ↑ 33%; Cmax ↑ 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.
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 doseshould be given twice daily. For infection resistant to integrase inhibitors, coadministration 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.
Multiple sclerosis		
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with dolutegravir is contraindicated.
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 wice 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 nducers 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%; Cmax ↓ 72% (Complex binding to polyvalent ions)	Magnesium- or aluminium-containing antacid should be taken well separated in time from dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39%; Cmax ↓ 37%; C24hours ↓ 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%; Cmax ↓ 57%; C24hours ↓ 56% (Complex binding to polyvalent ions)	
Multivitamins	Dolutegravir ↓ AUC ↓ 33%; Cmax ↓ 35% C24hours ↓ 32% (Complex binding to polyvalent ions)	
Antidiabetics		
Metformin	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; Cmax ↑ 66% Co-administered with dolutegravir 50 mg twice daily: Metformin ↑ AUC ↑ 145%; Cmax ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when given with dolutegravir, because the risk of lactic acidosis is increased in patients with moderate renal impairment due to increased metformin concentration.
Contraceptives		
Ethinylestradiol and norelgestromin	Dolutegravir ↔ Ethinylestradiol ↔ AUC ↑ 3%; Cmax ↓ 1% Norelgestromin ↔ AUC ↓ 2%; Cmax ↓ 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'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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below) and about effective contraceptive measures.

If a woman plans pregnancy, she should be given information about the benefits and the risks of continuing treatment with dolutegravir, to help her make an informed choice between the different antiretroviral regimens. Options for antiretroviral therapy will depend on the woman's treatment history and preference as well as local policies and treatment availability.

If feasible, women of childbearing potential should have pregnancy testing before starting dolutegravir.

Pregnancy

Women in the first trimester of pregnancy should be informed about the possibility of a small increased risk of neural tube defects with dolutegravir (see *Human and animal data on pregnancy*, below).

More than 1000 outcomes in women who took dolutegravir in the second and third trimester of pregnancy do not indicate increased risk of fetal or neonatal toxicity.

Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known if dolutegravir passes into human milk. In studies 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 (including those from the WHO) should be consulted before advising patients about breast-feeding. Preferred options may depend on local circumstances.

Fertility

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

Human and animal data on pregnancy

A birth outcome surveillance study in Botswana found a small increase of neural tube defects: an incident of 0.19% (7 cases in 3591 deliveries) to mothers taking dolutegravir-containing regimens at the time of conception compared to 0.11% (21 cases in 19 361) to women not taking dolutegravir.

However, Botswana does not have a national food folate fortification programme, which can significantly lower the prevalence of neural tube defects. Reports from countries which have national food folate fortification programmes show an incidence of neural tube defects in the general population ranging from 0.05 to 0.1%. The Botswana study found that dolutegravir-containing and efavirenz-containing antiretroviral regimens, when started later in pregnancy, have comparable pregnancy outcomes. Most neural tube defects occur in the first 4 weeks of fetal development. Therefore, any increased risk is likely to be associated with exposure to dolutegravir in the periconception period rather than later in the pregnancy.

Data from the Antiretroviral Pregnancy Registry do not indicate an increased risk of major birth defects in over 600 women taking dolutegravir during pregnancy, but these data are insufficient to address the risk of neural tube defects. To better understand the risk, research and surveillance are ongoing in pregnant women taking dolutegravir at the time of conception.

In animal reproductive toxicity studies, no adverse developmental outcomes, including neural tube defects, were identified. Dolutegravir crosses the placenta in animals (see section 5.3).

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 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 (≥ 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 reactivation 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 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	
Common	raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
Uncommon	hepatitis
Rare	acute hepatic failure, increased bilirubin (in combination with increased transaminases)
Skin and subcutaneous tissue disorders	
Common	rash, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon	arthralgia, myalgia
General disorders	
Common	fatigue
Investigations	
Common	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 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, 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).

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

Children

The limited data available for children and adolescents 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.

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

Pharmacotherapeutic group

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

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Pharmacodynamic effects

Antiviral activity in cell culture

The IC_{50} for dolutegravir in various lab-strains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7 to 2 nM. The IC_{50} 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 IC_{50} was 0.2 nM (range 0.02–2.14 nM). The mean IC_{50} 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.

Effect of human serum

In 100% human serum, the mean protein fold shift was 75-fold, resulting in protein adjusted IC90 of

0.064 µg/mL

Resistance in vitro

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. However, for Q148-mutations in combination with certain secondary mutations, the FC (fold-change as compared to wild-type virus) is 5-10 times or higher. The effect of the Q148-mutations (H/R/K) was verified in passage experiments with sitedirected mutants. In serial passage, 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 had a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Resistance in vivo

The most common clinically significant dolutegravir-resistance mutations are T66K, E92Q, G118R, E138K/A/T, G140S/A/G Q148H/R/K, N155H, R263K. The Q148H/R/K mutations reduce integrase strand transfer inhibitor (INSTI) susceptibility or virological response, while the other mutations listed contribute to reduced susceptibility in combination with other INSTI-resistance mutations.

Throughout the studies in previously untreated patients no cases of treatment-emergent primary resistance to the integrase inhibitors or to nucleoside reverse transcriptase occurred in patients treated with dolutegravir.

In treatment-experienced patients without prior exposure to integrase inhibitors statistically fewer subjects failed therapy with treatment-emergent integrase resistance on dolutegravir (4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003).

In a study of adult patients with prior failure to an integrase inhibitor, virologic response was associated with baseline integrase mutation pathway, as shown in the table below.

Baseline parameters	Dolutegravir 50 mg BID N=88*		
	n	Mean (SD) Plasma HIV-1 RNA log_{10} c/mL	Median
Derived integrase mutation group at Baseline with ongoing raltegravir/elvitegravir			
Primary mutation other than Q148H/K/R[a]	48	-1.59 (0.47)	-1.64
Q148+1 secondary mutation[b]	26	-1.14 (0.61)	-1.08
Q148+≥2 secondary mutations[b]	14	-0.75 (0.84)	-0.45

*Of 98 on raltegravir/elvitegravir as part of current failing regimen, 88 had detectable primary INI mutations at Baseline and at Day 8 Plasma HIV-1 RNA outcome for evaluation

a Included primary integrase resistance mutations N155H, Y143C/H/R, T66A, E92Q

b Secondary mutations from G140A/C/S, E138A/K/T, L74I.

In patients without a primary mutation detected at baseline (N=60) (i.e. raltegravir/elvitegravir not part of current failing therapy) there was a 1.63 log10 reduction in viral load at day 8.

In a study of paediatric participants experiencing virologic failure, 5/36 acquired integrase inhibitor substitution G118R. Of these five, 4 participants had additional integrase associated substitutions as follows:

L74M, E138E/K, E92E/Q and T66I. Four of the 5 participants with emergent G118R had phenotypic data available. Dolutegravir FC (fold change as compared to wildtype virus) for these four participants ranged from 6 to 25-fold.

For more detailed information reference is made to the current Stanford University HIV Drug Resistance Database.

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

The efficacy of dolutegravir has been shown in combination with various antiretroviral background regimens in previously untreated adult patients, patients treated previously with regimens that excluded integrase inhibitors and patients in whom an integrase inhibitor had failed (patients with HIV-1 resistant to integrase inhibitors, who were dosed with dolutegravir 50 mg twice daily). Virologic response rates ((HIVRNA<50 copies/ml) at week 48 ranged according to the population studied from 90% to 69%. In a study conducted in HIV-1 infected infants, children and adolescents aged ≥4 weeks to <18 years, mostly treatment-experienced, dosed once daily with dolutegravir film-coated tablets or dispersible tablets in combination regimens, 65.2% of the patients achieved virologic response (HIV-RNA<50 copies/ml) at week 48.

5.2 Pharmacokinetic properties

The absorption characteristics of Dolutegravir (as sodium) 50mg Tabletshave been determined in healthy volunteers as follows:

Characteristic	Arithmetic mean ± standard deviation
Maximum concentration (C_{max})	2.32 ± 0.65 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	45.7 ± 15.4 µg·h/mL
Time to attain maximum concentration (T_{max})	2.50 ± 1.51 hours

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		$AUC_{0-\infty}$	C_{max}	T_{max}
	Low fat	33% ↑	46% ↑	3 h
	Moderate fat:	41% ↑	52% ↑	4 h
	High fat:	66% ↑	67% ↑	5 h
	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 litres			
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				
Elimination half life	14 hrs			
Mean systemic clearance (Cl/F)	» 1 litre/hr			
% 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 *(in vitro)*				
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 log_{10} at day 11 for 50-mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

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 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 given once daily as film-coated and dispersible tablets in HIV-1 infected infants, children and adolescents aged ≥4 weeks to <18 years were evaluated in two studies. Steady state simulated plasma exposure at once daily weight band doses is summarized in the below table.

Weight band (kg)	Dolutegravir dosage form[a]	Once daily dose (mg)	PK parameter Geometric mean (90% CI)		
			Cmax (µg/mL)	AUC0-24h (µg*h/mL)	C24h (ng/mL)
3 to <6	DT	5	4.02 (2.12, 7.96)	49.4 (21.6, 115)	1070 (247, 3830)
6 to <10[b]	DT	10	5.90 (3.23, 10.9)	67.4 (30.4, 151)	1240 (257, 4580)
6 to <10[c]	DT	15	6.67 (3.75, 12.1)	68.4 (30.6, 154)	964 (158, 4150)
10 to <14	DT	20	6.61 (3.80, 11.5)	63.1 (28.9, 136)	719 (102, 3340)
14 to <20	DT	25	7.17 (4.10, 12.6)	69.5 (32.1, 151)	824 (122, 3780)
	FCT	40	6.96 (3.83, 12.5)	72.6 (33.7, 156)	972 (150, 4260)
20 to <25	DT	30	7.37 (4.24, 12.9)	72.0 (33.3, 156)	881 (137, 3960)
	FCT	50	7.43 (4.13, 13.3)	78.6 (36.8, 171)	1080 (178, 4690)
25 to <30	FCT	50	6.74 (3.73, 12.1)	71.4 (33.2, 154)	997 (162, 4250)
30 to <35	FCT	50	6.20 (3.45, 11.1)	66.6 (30.5, 141)	944 (154, 4020)
≥35	FCT	50	4.93 (2.66, 9.08)	54.0 (24.4, 118)	814 (142, 3310)
Target: Geometric Mean				46 (37-134)	995 (697-2260)

DT=dispersible tablet

FCT=film-coated tablet

a. The bioavailability of dolutegravir DT is ~1.6-fold dolutegravir FCT.

b. <6 months of age

c. ≥6 months of age

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 50 mg 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- 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.

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 1000 mg/kg.

In a juvenile toxicity study in rats, there were two pre-weanling deaths at 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, 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/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

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

Film coated:

Opadry II Brown 85F565142 (Polyvinyl alcohol, macrogol/polyethylene glycol, talc, titanium dioxide, red iron oxide and black iron oxide)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at temperatures not exceeding 30°C.

6.5 Nature and contents of container

HDPE Plastic Bottle (Box of 1 Bottle x 30 Tablets)

6.6 Instruction for use, handling and disposal

No special requirements

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

7. Imported and Distributed by:

Faberco Life Sciences Inc.

2nd & 3rd Flr., One Armstrong Bldg., Armstrong Avenue Corner Yosemite St., Moonwalk, Paranaque City, Metro Manila

8. DATE OF REVISION OF THE TEXT

May 2021

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph and Faberco Life Sciences Inc. at: safety@faberco.ph".

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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