

## **1. NAME OF THE MEDICINAL PRODUCT**

Dolutegravir Sodium 10 mg tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each dispersible tablet contains 10 mg dolutegravir (as sodium).

*Excipients with known effect:*

Each dispersible tablet also contains 29 mg of mannitol.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Dispersible tablets.

Pink-coloured, capsule-shaped, film-coated tablet debossed with 'K' and '1' and separated by a break-line on one side and another break-line on the other side.

The tablets can be divided into equal halves.

## **4. CLINICAL PARTICULARS**

### **4.1. Therapeutic indications**

Dolutegravir Sodium is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in children at least 4 weeks of age or older and weighing at least 3 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 issued by WHO) should be consulted.

### **4.2. Posology and method of administration**

Dolutegravir Sodium should be prescribed by a health care provider experienced in the management of HIV infection.

#### ***Posology***

##### ***Children weighing from 3 to 25 kg***

The dose of dolutegravir for children at least 4 weeks of age and weighing from 3 to 25 kg is based on the child's weight as shown in the table below. In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in children.

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## Dose recommendations for children weighing from 3 to 25 kg

Body weight	Dose	Number of tablets of Dolutegravir Sodium
3 kg to less than 6 kg	5 mg once daily	0.5
6 kg to less than 10 kg	15 mg once daily	1.5
10 kg to less than 14 kg	20 mg once daily	2
14 kg to less than 20 kg	25 mg once daily	2.5
20 kg to less than 25 kg*	30 mg once daily	3

\*For patients weighing at least 20 kg, the film-coated tablets containing 50 mg of dolutegravir are preferred. However, patients weighing between 20 and 25 kg who are unable to swallow tablets can take 30 mg (3 tablets) of dolutegravir dispersible tablets instead. The dolutegravir dispersible tablets and dolutegravir film-coated tablets are not bioequivalent: 30 mg of dolutegravir dispersible tablets corresponds to 50 mg of dolutegravir film-coated tablets.

The dose given in the table above should be doubled, meaning that the number of tablets shown in the table above should be taken twice daily instead of once a day, when dolutegravir is used with medicines such as efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin (see section 4.5).

### *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).

The tablets should be dispersed in drinking water before administration of the dose. Each tablet should be dispersed in a minimum of 10 mL of drinking water; the maximum volume of water recommended for dispersion of a dose is 50 mL.

#### *Instructions for use*

1. The required amount of drinking water should be placed in a small clean cup and the dolutegravir tablets added to it.
2. The cup should be gently swirled until the tablets disperse, and the patient should drink all the mixture immediately.
3. The cup should be rinsed with an additional 10 mL of water, which the patient should drink to ensure that the patient takes the full dose.

#### **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 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, generalized 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 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. Its 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*

Dolutegravir Sodium contains mannitol, which may have a mild laxative effect.

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). 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).

### **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  $C_{max}$ , concentration at end of dosing interval as  $C_T$ ).

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
<b>Antimicrobials</b>		
Antiretrovirals		
<i>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</i>		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71%; C <sub>max</sub> ↓ 52%; C <sub>T</sub> ↓ 88%  Etravirine ↔ (induction of UGT1A1 and CYP3Aenzymes)	Etravirine 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 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%; C <sub>max</sub> ↑ 7%; C <sub>T</sub> ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25%; C <sub>max</sub> ↓ 12%; C <sub>T</sub> ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57%; C <sub>max</sub> ↓ 39%; C <sub>T</sub> ↓ 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 doses 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 doses 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 <sub>max</sub> ↑ 13%; C <sub>T</sub> ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
<i>Nucleoside reverse transcriptase inhibitors (NRTI)</i>		
Tenofovir disoproxil	Dolutegravir ↔ AUC ↑ 1%; C <sub>max</sub> ↓ 3%; C <sub>T</sub> ↓ 8% Tenofovir ↔	No dose adjustment is necessary.

<b>Medicines by therapeutic area</b>	<b>Interaction Changes shown as geometric mean</b>	<b>Recommendations on co-administration</b>
<i>Protease inhibitors (PIs)</i>		
Atazanavir	Dolutegravir ↑ AUC ↑ 91%; C <sub>max</sub> ↑ 50%; C <sub>T</sub> ↑ 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 <sub>max</sub> ↑ 34%; C <sub>T</sub> ↑ 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 <sub>max</sub> ↓ 47%; C <sub>T</sub> ↓ 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 twicedaily.  For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Fosamprenavir/ritonavir	Dolutegravir ↓ AUC ↓ 35%; C <sub>max</sub> ↓ 24%; C <sub>T</sub> ↓ 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	<u>Dolutegravir</u> ↓ AUC ↓ 22%; C <sub>max</sub> ↓ 11%; C <sub>24hours</sub> ↓ 38% (induction of UGT1A1 and CYP3Aenzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4%; C <sub>max</sub> ↔ 0%; C <sub>24hours</sub> ↓ 6%	No dose adjustment is necessary.
Antivirals against hepatitis C		
Daclatasvir	Dolutegravir ↔ AUC ↑ 33%; C <sub>max</sub> ↑ 29%; C <sub>T</sub> ↑ 45% Daclatasvir ↔	No dose adjustment is necessary.
<b>Medicines by therapeutic area</b>	<b>Interaction Changes shown as geometric mean</b>	<b>Recommendations on co- administration</b>
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%; C <sub>max</sub> ↓ 43%; C <sub>T</sub> ↓ 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 doses should be given twice daily. For infection resistant to integrase inhibitors, co- administration of dolutegravir and rifampicin should be avoided.



Rifabutin	Dolutegravir ↔ AUC ↓ 5%; C <sub>max</sub> ↑ 16%; C <sub>T</sub> ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
<b>Antifungals</b>		
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.
<b>Multiple sclerosis</b>		
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.
<b>Antiepileptics</b>		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49%; C <sub>max</sub> ↓ 33%; C <sub>T</sub> ↓ 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.
<b>Medicines by therapeutic area</b>	<b>Interaction Changes shown as geometric mean</b>	<b>Recommendations on co-administration</b>
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.
<b>Antiarrhythmics</b>		

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.
<b>Antacids and supplements</b>		
Magnesium- or aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74%; C <sub>max</sub> ↓ 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%; C <sub>max</sub> ↓ 37%; C <sub>24hours</sub> ↓ 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 <sub>max</sub> ↓ 57%; C <sub>24hours</sub> ↓ 56% (Complex binding to polyvalent ions)	
Multivitamins	Dolutegravir ↓ AUC ↓ 33%; C <sub>max</sub> ↓ 35% C <sub>24hours</sub> ↓ 32% (Complex binding to polyvalent ions)	
<b>Antidiabetics</b>		
Metformin	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; C <sub>max</sub> ↑ 66% Co-administered with dolutegravir 50 mg twice daily: Metformin ↑ AUC ↑ 145%; C <sub>max</sub> ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when given with dolutegravir, because the risk of lactic acidosis is increased in patients with moderate renal impairment due to increased metformin concentration.
<b>Contraceptives</b>		
Ethinylestradiol and norelgestromin	Dolutegravir ↔ Ethinylestradiol ↔ AUC ↑ 3%; C <sub>max</sub> ↓ 1% Norelgestromin ↔ AUC ↓ 2%; C <sub>max</sub> ↓ 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.
<b>Corticosteroids</b>		

Prednisone	Dolutegravir ↔ AUC ↑ 11%; C <sub>max</sub> ↑ 6%; C <sub>T</sub> ↑ 17%	No dose adjustment is necessary.
<b>Medicines by therapeutic area</b>	<b>Interaction Changes shown as geometric mean</b>	<b>Recommendations on co-administration</b>
<b>Drug abuse</b>		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2%; C <sub>max</sub> ↔ 0%; C <sub>T</sub> ↓ 1%	No dose adjustment is necessary.
<b>Herbal products</b>		
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 ( $\geq 1/10$ ), common (1/100 to 1/10), uncommon (1/1000 to 1/100), rare (1/10 000 to 1/1000), and very rare ( $< 1/10\ 000$ ).

#### Immune system disorders

Uncommon Hypersensitivity (see section 4.4)

Immune 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

#### 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  $\mu\text{mol/L}$  occurred after 48 weeks of treatment. Creatinine increases were comparable between various background regimens. These changes are not considered clinically relevant since they do not reflect a change in glomerular filtration rate.

#### *Co-infection with hepatitis B or C*

In clinical studies, 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<sub>50</sub> for dolutegravir for clinical isolates showed no 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<sub>50</sub> was 0.2 nM (range 0.02–2.14 nM). The mean IC<sub>50</sub> 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 IC<sub>90</sub> 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 site-directed 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, and 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 <sub>10</sub> c/mL	Median
Derived integrase mutation group at Baseline with ongoing raltegravir/ elvitegravir			
Primary mutation other than Q148H/K/R <sup>a</sup>	48	- 1 . 5 9 (0.47)	- 1 . 6 4
Q148+1 secondary mutation <sup>b</sup>	26	- 1 . 1 4 (0.61)	- 1 . 0 8
Q148+≥2 secondary mutations <sup>b</sup>	14	- 0 . 7 5 (0.84)	- 0 . 4 5

\*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

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

<sup>b</sup> 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 log<sub>10</sub> 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 ((HIV-RNA<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 week48.

**2. Pharmacokinetic properties**

The absorption characteristics of Dolutegravir Sodium have been determined after administration of single tablets (containing 10 mg dolutegravir) in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value* (± standard deviation)
Maximum concentration (C <sub>max</sub> )	1270 ± 245 ng/ml
Area under the curve (AUC <sub>0-inf</sub> ), a measure of the extent of absorption	22293 ± 5727 ng·h/ml
Time to attain maximum concentration (t <sub>max</sub> )	0.86 ± 0.52 h

\* Arithmetic mean

Pharmacokinetics of dolutegravir

Dolutegravir									
<b>General</b>									
	PK similar for healthy and HIV-infected subjects. Low to moderate PK variability								
<b>Absorption</b>									
Absolute bioavailability	Not known								
Oral bioavailability	At least 32%								
Food effect	<table border="1"> <thead> <tr> <th></th> <th>AUC(0-∞)</th> <th>C<sub>max</sub></th> <th>T<sub>max</sub></th> </tr> </thead> <tbody> <tr> <td>Low fat</td> <td>33%-</td> <td>46%-</td> <td>3 h</td> </tr> </tbody> </table>		AUC(0-∞)	C <sub>max</sub>	T <sub>max</sub>	Low fat	33%-	46%-	3 h
		AUC(0-∞)	C <sub>max</sub>	T <sub>max</sub>					
Low fat	33%-	46%-	3 h						



	<table border="1"> <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> <p>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.</p>	Moderate fat:	41%-	52%-	4 h	High fat:	66%-	67%-	5 h
Moderate fat:	41%-	52%-	4 h						
High fat:	66%-	67%-	5 h						
<b>Distribution</b>									
Volume of distribution (mean)	17 to 20 L								
Plasma protein binding <i>in vitro</i>	> 99%, increase in unbound fraction with low serum albumin(as in moderate hepatic impairment)								
Tissue distribution	CSF: mean 18 ng/mL (comparable to unbound plasma concentration, and > IC50) Vaginal, cervical tissue, cervicovaginal fluid: 6-10% Semen: 7% Rectal tissue: 17% (each of corresponding plasma levels at steady state)								
<b>Metabolism</b>									
	Hepatic metabolism: glucuronidation via UGT1A1 minor pathway CYP3A								
Active metabolite(s)	N/A								
<b>Elimination</b>									
Elimination half life	14 h								
Mean systemic clearance(CI/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								
<b>Pharmacokinetic linearity</b>	Depending on dose and formulation. For tablets: Dose-proportional increases from 25 to 50 mg								
<b>Drug interactions (<i>in vitro</i>)</b>									

Transporters	Inhibition of OCT2, MATE-1, OAT3 and OAT1 (clinical relevance of the latter unlikely) No relevant inhibition of P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4 No substrate of human OATP 1B1, OATP 1B3 or OCT 1
Metabolizing enzymes	No relevant inhibition of (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyltransferase (UGT)1A1 or UGT2B7 No induction of CYP1A2, CYP2B6 or CYP3A4

**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<sub>10</sub> 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 <sup>a</sup>	Once daily dose (mg)	PK parameter Geometric mean (90% CI)		
			C <sub>max</sub> (µg/mL)	AUC <sub>0-24h</sub> (µg*h/mL)	C <sub>24h</sub> (ng/mL)
3 to <6	DT	5	4.02 (2.12, 7.96)	49.4 (21.6, 115)	1070 (247, 3830)
6 to <10 <sup>b</sup>	DT	10	5.90 (3.23, 10.9)	67.4 (30.4, 151)	1240 (257, 4580)
6 to <10 <sup>c</sup>	DT	15	6.67	68.4	964

			(3.75, 12.1)	(30.6, 154)	(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)
<b>Target: Geometric Mean</b>				<b>46 (37-134)</b>	<b>995 (697-2260)</b>

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.

#### 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-weaning 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<sup>2</sup> equivalent dose for a clinical dose of 50 mg twice daily.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Core tablet: Mannitol

Microcrystalline cellulose

Sodium starch glycolate

Povidone

Silicified microcrystalline cellulose Crospovidone

Calcium sulphate dihydrate

Strawberry cream flavour Sucralose

Sodium stearyl fumarate

Film coat: Hypromellose

Titanium dioxide

Macrogol/polyethylene glycol

Iron oxide red

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

24 months

### **6.4. Special precautions for storage**

Do not store above 30°C. Store in the original package to protect from moisture. Keep the bottle tightly closed. Avoid excursions above 30°C.

### **6.5. Nature and contents of container**

White, round, HDPE bottle with polypropylene child-resistant closure with pulp and white printed heat sealliner. The bottle may or may not contain a 1 g silica gel sachet. Pack size: 90 tablets.

### **6.6. Special precautions for disposal and other handling**

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

## **7. MARKETING AUTHORISATION HOLDER**

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**8. MARKETING AUTHORISATION NUMBER**

TAN 22 HM 0328

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21/09/2022

**10. DATE OF REVISION OF THE TEXT**

