1. NAME OF THE MEDICINAL PRODUCT
VIDOTEG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.

3. PHARMACEUTICAL FORM
Light-brown to brown, film-coated, capsule-shaped tablet, debossed with “RL75” on one side and a break line on the other side.
The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
[HA708 trade name] is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20 kg. Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.
[HA708 trade name] may also be used in these patients as part of a regimen for post-exposure prophylaxis for HIV. 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
[HA708 trade name] should be prescribed by a health care provider experienced in the management of HIV infection.

Posology
Treatment of HIV infection
Adults
The dose in adults with HIV-1 infection not resistant to integrase inhibitors is 1 tablet of [HA708 trade name] (50 mg dolutegravir) once daily.
The dose should be 1 tablet twice daily if:
- dolutegravir is used with medicines that reduce dolutegravir exposure 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 1 tablet (50 mg dolutegravir) once daily.
The dose should be 1 tablet (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 to recommend a dose 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. Other formulations should be preferred.

Post-exposure prophylaxis (PEP)

The recommended dose of [HA708 trade name] as part of a regimen for PEP in adults and children weighing more than 20 kg is the same as for treatment of HIV infection (above).

PEP should start as early as possible after exposure and ideally within 72 hours of exposure, and is given for a total of 28 days.

Dosing in special populations

Elderly

Based on limited data, 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 that 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 just 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

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. A two-drug regimen of dolutegravir and lamivudine once daily (as explored in the GEMINI 1 and GEMINI 2 studies) is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine

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, 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 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, including with regimens that incorporate dolutegravir. 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. Monitoring of blood lipids and glucose should be carried out as clinically appropriate and in line with operative HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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 such as 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, and the transporters P-gp and BCRP; therefore, medicines that induce the function of these proteins may decrease dolutegravir plasma concentration and reduce its therapeutic effect. Conversely, giving dolutegravir with other medicinal products that inhibit their function may increase dolutegravir plasma concentration (see table, below).

Effects of dolutegravir on other agents

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on *in vivo* and in vitro data, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of major enzymes or transporters such as CYP3A4, CYP2C9 and P-gp (see section 5.2).

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 and/or MATE-1 (e.g. fampridine [also known as dalfampridine], metformin) (see the table below).

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

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_{τ}).

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%; C_{max} ↓ 52%; C_{τ} ↓ 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 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).

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11%; C_{max} ↑ 7%; C_{τ} ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25%; C_{max} ↓ 12%; C_{τ} ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57%; C_{max} ↓ 39%; C_{τ} ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with efavirenz. In paediatric patients the weight-based once-daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include efavirenz should be considered.
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with nevirapine. In paediatric patients the weight-based once-daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12%; C_{max} ↑ 13%; C_{τ} ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTI)		
Tenofovir disoproxil	Dolutegravir ↔ AUC ↑ 1%; C_{max} ↓ 3%; C_{τ} ↓8% Tenofovir ↔	No dose adjustment is necessary.
Protease inhibitors (PIs)		
Atazanavir	Dolutegravir ↑ AUC ↑ 91%; C_{max} ↑ 50%; C_{τ} ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62%; C_{max} ↑ 34%; C_{τ} ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Tipranavir/ritonavir	Dolutegravir ↓ AUC ↓ 59%; C_{max} ↓ 47%; C_{τ} ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with tipranavir/ritonavir. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Fosamprenavir/ ritonavir	Dolutegravir ↓ AUC ↓ 35%; C_{max} ↓ 24%; C_{τ} ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. For infection resistant to integrase inhibitors, alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22%; C_{max} ↓ 11%; $C_{24hours}$ ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4%; C_{max} ↔ 0%; $C_{24hours}$ ↓ 6%	No dose adjustment is necessary.
Antivirals against hepatitis C		
Daclatasvir	Dolutegravir ↔ AUC ↑ 33%; Cmax ↑ 29%; C_{τ} ↑ 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%; C_{max} ↓ 43%; C_{τ} ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with rifampicin. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, co-administration of dolutegravir and rifampicin should be avoided.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Rifabutin	Dolutegravir ↔ AUC ↓ 5%; C_{max} ↑ 16%; C_{τ} ↓ 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.
Antacids and supplements		
Magnesium- or aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74%; C_{max} ↓ 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_{max} ↓ 37%; $C_{24hours}$ ↓ 39% (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Iron supplements	Dolutegravir ↓ AUC ↓ 54%; C_{max} ↓ 57%; $C_{24hours}$ ↓ 56% (Complex binding to polyvalent ions)	
Multivitamins	Dolutegravir ↓ AUC ↓ 33%; C_{max} ↓ 35% $C_{24hours}$ ↓ 32% (Complex binding to polyvalent ions)	
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.
Antidiabetics		
Metformin	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; C_{max} ↑ 66% Co-administered with dolutegravir 50 mg twice daily: Metformin ↑ AUC ↑ 145%; C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when given with dolutegravir, because the risk of lactic acidosis is increased in patients with moderate renal impairment due to increased metformin concentration.
Antiepileptics		

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Carbamazepine	Dolutegravir ↓ AUC ↓ 49%; Cmax ↓ 33%; Cτ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when given with carbamazepine. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to carbamazepine should be used in patients with infection resistant to integrase inhibitors.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with these enzyme inducers. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to these medicines that are not enzyme inducers should be used in patients with infection resistant to integrase inhibitors.
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.
Multiple sclerosis medicines		
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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential
There has been concern about the potential risk of neural tube defects with dolutegravir (see below). Dolutegravir-based regimens can be recommended for HIV treatment in women of childbearing potential, as the overall benefits are considered likely to outweigh the risks. Use of effective contraceptive measures, and pregnancy testing before beginning treatment, may be considered. Health care providers should discuss any concerns, and the benefits and risks of available treatment options, with women who are planning to become pregnant.

Pregnancy
Dolutegravir may be used for the treatment of HIV in pregnancy.
There has been concern about the possibility of a small increased risk of neural tube defects with dolutegravir taken in the periconceptional period (see *Human and animal data on pregnancy*, below). However, it is unclear that the risks with dolutegravir-based regimens are genuinely greater than for alternative options, and the benefits of effective HIV treatment with dolutegravir are considered likely to outweigh the risks.
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.

Breast-feeding
Dolutegravir is excreted in human milk in small amounts (a median dolutegravir breast milk to maternal plasma ratio of 0.033 has been shown). There is insufficient information on the effects of dolutegravir in neonates/infants.
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.
Subsequent update of the Botswana study up to March 2022 reported 10 cases among 9 460 deliveries to mothers taking dolutegravir-containing regimens at conception compared to 25 cases

among 23 664 deliveries to women using regimens not containing dolutegravir (both 0.11%).
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). In pregnant women living with HIV, the median fetal umbilical cord concentration of dolutegravir was approximately 1.3-fold greater compared with the maternal peripheral plasma concentration

4.7 Effects on ability to drive and use machines

Patients should be informed that dolutegravir can cause dizziness. The patient's clinical status as well as dolutegravir's side effects should be considered when 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 (at least 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)

Metabolism and nutrition disorders

Common	weight gain

Psychiatric disorders

Common	insomnia, abnormal dreams, depression, anxiety
Uncommon	panic attack, suicidal ideation or suicide attempt (particularly in patients with history of depression or psychiatric illness; deaths from suicide have occurred)

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/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 an inflammatory reaction to asymptomatic or residual opportunistic infections may arise at the start of combination antiretroviral therapy. 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 authorization of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorization holder or, where applicable, via the national reporting system https://pv.pharmacyboardkenya.org/

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, integrase inhibitors, ATC code: J05AJ03.

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 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_{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 IC_{90} 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. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to most of these primary mutations in experiments with site directed mutants, dolutegravir susceptibility is still unchanged (FC <2 vs wild-type virus). 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. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

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). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected in vitro.
In the presence of integrase class-resistance (VIKING-3 study) the following mutations were selected in 32 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimized background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H
(n=1) and E157E/Q (n=1). Treatment emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects experienced PDVF between weeks 24 and 48, and 2 of these 5 had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2). Treatment-emergent mutations observed in another study in 30 subjects with primary genotypic resistance to integrase inhibitors at screening given dolutegravir plus optimised background therapy were consistent with those in the VIKING-3 study.
In paediatric patients with prior failed therapies, but naïve to the integrase class, the integrase inhibitor substitution G118R was observed in 5/159 patients treated with dolutegravir, given in combination with an investigator selected background regimen. 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%(response was, however, lower in the presence of the Q148 mutation at baseline, especially if there were also 2 or more secondary mutations).
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. In participants experiencing virologic failure, 5/36 acquired integrase inhibitor substitution G118R, mostly with additional integrase associated substitutions. Dolutegravir FC (fold change as compared to wildtype virus) for participants with phenotypic data available ranged from 6 to 25-fold.

5.2 Pharmacokinetic properties

Absorption of [HA708 trade name]
The absorption characteristics of [HA708 trade name] have been determined after administration of a single dose tablet in healthy subjects in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value (± standard deviation)
	Dolutegravir
Maximum concentration (Cmax)	2.667 ± 0.638 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	40.808 ± 13.097 µg·h/mL
Time to attain maximum concentration (T_{max})	2.10 ± 1.20 h

Pharmacokinetics of dolutegravir

	Dolutegravir
General	
	PK similar for healthy and HIV-infected subjects. Low to moderate PK variability
Absorption	
Absolute bioavailability	Not known
Oral bioavailability	At least 32%. The relative bioavailability of dispersible tablets is approximately 1.6-fold higher than film-coated tablets.
Food effect	<table><tr><th></th><th>AUC (0-∞)</th><th>Cmax</th><th>Tmax</th></tr><tr><td>Low fat</td><td>33%□</td><td>46%□</td><td>3 h</td></tr><tr><td>Moderate fat:</td><td>41%□</td><td>52%□</td><td>4 h</td></tr><tr><td>High fat:</td><td>66%□</td><td>67%□</td><td>5 h</td></tr></table> Increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, it is recommended that patients infected with HIV resistant to integrase inhibitors take dolutegravir with food.
Distribution	
Volume of distribution (mean)	17 to 20 L

Plasma protein binding *in vitro*	> 99%, increase in unbound fraction with low serum albumin (as in moderate hepatic impairment)
Tissue distribution	CSF: mean 18 ng/mL (comparable to unbound plasma concentration, and > IC50) Vaginal, cervical tissue, cervicovaginal fluid: 6-10% Semen: 7% Rectal tissue: 17% (each of corresponding plasma levels at steady state)
Metabolism	
	Hepatic metabolism: glucuronidation via UGT1A1 minor pathway CYP3A
Active metabolite(s)	N/A
Elimination	
Elimination half life	14 h
Mean systemic clearance (Cl/F)	□1 L/h
% of dose excreted in urine	32% in total;
	<1% unchanged, 19% as ether glucuronide Other metabolites; N-dealkylation metabolite and metabolite formed by oxidation at the benzylic carbon
% of dose excreted in faeces	53% is excreted unchanged in the faeces
Pharmacokinetic linearity	Depending on dose and formulation. For film-coated tablets: dose-proportional increases from 25 to 50 mg
Drug interactions *(in vitro*)	
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 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 FCT	25 40	7.17 (4.10, 12.6) 6.96 (3.83, 12.5)	69.5 (32.1, 151) 72.6 (33.7, 156)	824 (122, 3780) 972 (150, 4260)
20 to <25	DT FCT	30 50	7.37 (4.24, 12.9) 7.43 (4.13, 13.3)	72.0 (33.3, 156) 78.6 (36.8, 171)	881 (137, 3960) 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 1000 mg/kg daily (around 25 times normal human clinical exposure based on AUC). Oral administration of dolutegravir to pregnant rats at similar doses 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^2 equivalent dose for a clinical dose of 50 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:
Mannitol
Microcrystalline cellulose
povidone
sodium starch glycolate
sodium stearyl fumarate
talc
Magnesium stearate.

Film coat:
Polyvinyl alcohol partially hydrolysed
Titanium dioxide
Macrogol/polyethylene glycol
Talc
Iron oxide yellow
Iron oxide red.
This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened bottle: 36 months
Unused tablets should be discarded 30 days after first opening of the bottle. When the bottle is first opened this “Discard after date” should be written on the bottle label in the place provided. (This is onlyapplicable to pack size of 30 tablets).
Unused tablets should be discarded 90 days after first opening of the bottle. When the bottle is first opened this “Discard after date” should be written on the bottle label in the place provided. (This is onlyapplicable to pack size of 90 tablets).

6.4 Special precautions for storage
Do not store above 30 ^{0}C.

6.5 Nature and contents of container
White, opaque HDPE bottle with a white, opaque polypropylene screw /child-resistant closure.

Pack sizes: 30 and 90 film-coated tablets.

7. MARKETING AUTHORIZED HOLDER
Sun Pharmaceutical Industries Limited
Sun House, 201 B/1
Western Express Highway
Goregoan (East)
Mumbai 400 063
India
Tel. No.: (+91 22) 4324 4324
Fax. No.: (+91 22) 4324 4343

8. MARKETING AUTHORIZATION NUMBER
H2022/CTD7816/14966

9. DATE OF AUTHORIZATION
18/04/2023

10. DATE OF REVISION OF THE TEXT
18/04/2023