SUMMARY OF PRODUCT CHARACTERISTICS

DOLUTEGRAVIR TABLETS 50 mg

Rx Only

1. Name of the Finished Pharmaceutical Product

Dolutegravir Tablets 50 mg

2. Qualitative and quantitative composition

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dolutegravir Tablets are reddish brown colored, round, biconvex, film coated tablets debossed with 'T over 50' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Dolutegravir Tablets is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age.

4.2 Posology and method of administration

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

Posology

Adults

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

The dose should be 50 mg twice daily if:

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

When HIV-1 genotype testing is available and for patients whose treatment options are limited (fewer than 2 active antiretrovirals) due to advanced multi-class resistance, a higher dose of dolutegravir may be considered. Such resistance may include Q148 + 2 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.

Adolescents weighing at least 40 kg

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

Children

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

Elderly

There are limited data available on the use of dolutegravir in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2).

Renal impairment

No dose adjustment is needed for patients with renal impairment. The use of dolutegravir has not been studied in patients on dialysis but the dose is not expected to be different for these patients.

Hepatic impairment

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

Missed dose

If the patient misses a dose of dolutegravir, the patient should take it as soon as possible, provided the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and take the next dose at the usual time.

Method of administration

Oral use.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Effective antiviral therapy can substantially reduce the risk of sexual transmission. However, the 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 its activity is considerably reduced for viral strains with Q148 + ≥ 2 secondary mutations from G140A/C/S, E138A/K/T, L74I. Dolutegravir's contribution to efficacy is uncertain when it is used to treat HIV-1 with this type of resistance to integrase inhibitors.

Hypersensitivity reactions

Hypersensitivity reactions reported with dolutegravir are characterised by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect agents should be discontinued immediately if hypersensitivity reactions develop (including severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, and angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency when starting combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions occur within the first few weeks or months of starting CART. Examples of such conditions are cytomegalovirus retinitis, generalised or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treated when necessary. Autoimmune disorders (such as Graves' disease) have also been reported in the setting of immune reconstitution, but the reported time to onset is more variable and these events can occur many months after starting treatment.

Raised liver enzymes, consistent with immune reconstitution syndrome, occurred in some patients who also had hepatitis B or C infection at the start of dolutegravir therapy. Monitoring of liver function is recommended in patients with hepatitis B or C co-infection. Particular care

should be taken in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients.

Opportunistic infections

Patients should be advised that antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection.

Osteonecrosis

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

Excipient

Each tablet also contains 3.976 mg of sodium which is less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on dolutegravir

Factors that lower plasma concentration of dolutegravir should be avoided in the presence of HIV-1 resistant to integrase inhibitors. This includes concomitant use of medicines that reduce blood levels of Dolutegravir (e.g. magnesium- or aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain antiepileptic medicines) (see table, below).

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

Effects of dolutegravir on other agents

Dolutegravir can increase metformin concentrations.

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

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE-1). In patients, creatinine clearance decreased by 10–14% (secretory fraction is dependent on OCT2 and MATE-1 transport). Dolutegravir may increase plasma concentrations of medicines whose excretion involves OCT2 or MATE-1 (e.g. dofetilide, metformin) (see table, below).

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

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the following table; the pharmacokinetic data reflect studies in adults.

Interaction table

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

Drug interactions

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Antimicrobials		
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors		

Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine decreased plasma dolutegravir concentration, which may result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir (see further below in table).
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75% 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 ↓	The recommended adult dose of

	(Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	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% Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors (NRTI)		
Tenofovir disoproxil	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% Cτ ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors (PIs)		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121%	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in

	Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	combination with atazanavir because data are not available.
Tipranavir/ritonavir	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% Cτ ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with tipranavir/ritonavir. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include Tipranavir/ritonavir should be considered.
Fosamprenavir/ ritonavir	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% Cτ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. For infection resistant to integrase inhibitors, alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% 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% C24 ↓ 6%	No dose adjustment is necessary.
Antivirals against hepatitis C		

Boceprevir	Dolutegravir ↔ AUC ↑ 7% C_{max} ↑ 5% C_{τ}↑ 8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Elbasvir/grazoprevir Glecaprevir/pibrentasvir Ledipasvir/sofosbuvir Ombitasvir/paritaprevir Ombitasvir/paritaprevir/ dasabuvir Simeprevir Sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/ voxilaprevir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.
Antibiotics		
Rifampicin	Dolutegravir ↔ AUC ↓ 54%; Cmax ↓ 43%; Cτ ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with rifampicin. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, co-administration of dolutegravir and rifampicin should be avoided.

Rifabutin	Dolutegravir ↔ AUC ↓ 5%; Cmax ↑ 16%; Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Antifungals		
Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Antiepileptics		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49%; Cmax ↓ 33%; Cτ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when given with carbamazepine. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to carbamazepine should be used in patients with infection resistant to integrase inhibitors.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with these enzyme inducers. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to these medicines that are not enzyme inducers should be used in patients with infection resistant to integrase inhibitors.

Antiarrhythmics		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration
Azole anti-fungal agents		
Ketoconazole Fluconazole Itraconazole 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/ aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% $C_{24hours}$ ↓ 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

Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% $C_{24hours}$ ↓ 56% (Complex binding to polyvalent ions)	hours before).
Multivitamin	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% $C_{24hours}$ ↓ 32% (Complex binding to polyvalent ions)	
Antidiabetics		
Metformin	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; Cmax ↑ 66% Co-administered with dolutegravir 50 mg twice daily: Metformin ↑ AUC ↑ 145%; 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.
Contraceptives		

Ethinyl estradiol (EE) 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% C_{max} ↔ 0% Cτ ↓ 1%	No dose adjustment is necessary of either agent.
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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on the use of dolutegravir in pregnant women are limited and its effect on human pregnancy is unknown. In animal studies, dolutegravir crossed the placenta; the studies do not indicate direct or indirect harmful effects.

Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known if dolutegravir passes into human milk. Animal studies show that dolutegravir appears in milk. In rats receiving a single oral dose of 50 mg/kg 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than blood.

Current recommendations on HIV and breast-feeding (e.g. those from the WHO) should be consulted before advising patients on this matter.

Preferred options may vary depending on the local circumstances.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Immune system disorders	
Uncommon	hypersensitivity (see section 4.4) immune reactivation syndrome (see section 4.4 and also described below)
Psychiatric disorders	

Common	insomnia abnormal dreams depression
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	flatulence upper abdominal pain abdominal pain abdominal discomfort
Hepatobiliary disorders	
Uncommon	hepatitis
Skin and subcutaneous tissue disorders	
Common	rash pruritus
Musculoskeletal and connective tissue disorders	
Uncommon	arthralgia myalgia
General disorders	
Common	Fatigue
Investigations	
Common	raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) raised creatine kinase

Description of selected adverse reactions

Changes in serum creatinine

Serum creatinine can increase in the first week of treatment with dolutegravir and then remain stable. A mean change from baseline of 9.96 μmol/litre was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These

changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C

In clinical studies, the safety 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 withdrawn.

Immune reactivation syndrome

In HIV patients with severe immune deficiency at the time of initiation 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 reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Children

Based on limited available data in children and adolescents (aged 6 to 18 years and weighing at least 15 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

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 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 IC50 for dolutegravir in various lab-strains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7 to 2 nM. Similar IC50 were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC50 was 0.2 nM (range 0.02–2.14 nM). The mean IC50 for three HIV-2 isolates was 0.18 nM (range 0.09–0.61 nM).

Antiviral activity in combination with other antiviral agents

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

Effect of human serum

In 100% human serum, the mean protein fold shift was 75-fold, resulting in protein adjusted IC90 of 0.064 ug/mL.

Resistance

Resistance in vitro

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

Using clinical isolates of subtype B, C and A/G the integrase substitution R263K and G118R (in C and A/G) R263K was reported from two ART-experienced, integrase-inhibitor-naive patients with subtypes B and C in the clinical program, but without effects on dolutegravir susceptibility *in vitro*. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10), but was not detected in patients receiving dolutegravir in the Phase III program.

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the *in vitro* susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase-inhibitor-associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site-directed mutants, dolutegravir susceptibility is still unchanged (FC < 2 vs wild type virus), except in

the case of Q148-mutations, where a FC is 5–10 or higher with combinations of certain secondary mutations. The effect by the Q148-mutations (H/R/K) was also verified in passage experiments with site-directed mutants. In serial passage with strain NL432, starting with site-directed mutants harbouring N155H or E92Q, further selection of resistance did not occur (FC unchanged around 1). In contrast, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen with a consequent increase of FC to values > 10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

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

Resistance in vivo

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

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

In the presence of integrase-inhibitor class-resistance the following mutations were selected in 32 patients with protocol-defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimised background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and E157E/Q (n=1). Treatment-emergent integrase-inhibitor-resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects 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 in 30 subjects with primary genotypic resistance to integrase inhibitors at screening who were treated with dolutegravir (plus optimised background therapy) were consistent with these findings.

Effects on electrocardiogram

No relevant effects were seen on the QTc interval, with doses exceeding the clinical dose by approximately three-fold.

Clinical efficacy and safety

Previously untreated patients

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

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

Patients treated previously with regimens that excluded integrase inhibitor

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

Patients in whom treatment that included an integrase inhibitor had failed (with HIV-1 resistant to integrase inhibitors)

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

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

subsequent treatment of all patients with with dolutegravir 50 mg twice daily and optimised background therapy, 40% of patients had fewer than 50 copies/mL at week 48.

Paediatric population

A study in children and adolescents aged up to 18 years investigated the pharmacokinetics, tolerability and efficacy of dolutegravir given in a dose of around 1 mg/kg daily in combination with other antiretrovirals. Patients were divided into two cohorts, each including 23 patients (the first cohort included adolescents aged from 12 to 18 years and the second cohort included patients aged from 6 years to 12 years). The viral load after 24 weeks was fewer than 50 copies/ml in 70% of patients in the first cohort and 61% in the second cohort.

5.2 Pharmacokinetic properties

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. Following single dose administration of Dolutegravir Tablets 50 mg in healthy volunteers, the mean (± SD) dolutegravir Cmax was 2467 ng/ml (± 665) and the mean (SD) AUC0-inf was 53704 ng.hour/ml (± 18795) and AUC0-t was 50692 ng.hour/ml (±16877). The mean (± SD) dolutegravir tmax was 2.45 (± 1.29) hours.

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablets, in general, dolutegravir exhibited non-linear pharmacokinetics with less than dose- proportional increases in plasma exposure from 2 to 100 mg; however, increase in dolutegravir exposure appears dose-dependent from 25 to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg once daily.

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median Tmax at 2 to 3 hours post dose for tablet formulation.

Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir AUC(0-∞) by 33%, 41%, and 66%, increased Cmax by 46%, 52%, and 67%, prolonged Tmax to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These 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.

The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (> 99%) to human plasma proteins based on *in vitro* data. The apparent volume of distribution is 17 to 20 litres in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (< 35 g/litre) as seen in subjects with moderate hepatic impairment.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve patients on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/ml (comparable to unbound plasma concentration, and above the IC_{50}).

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6–10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of

unchanged active substance is low (< 1% of the dose). Of the total oral dose, 53% is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Excretion in the urine accounts for 33% of the total oral dose as ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6%), and a metabolite formed by oxidation at the benzylic carbon (3.0%).

Drug interactions

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50> 50 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Therefore, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of major enzymes or transporters.

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Elimination

Dolutegravir has a terminal half-life of about 14 hours. The apparent oral clearance (CL/F) is approximately 1 litre/hour in HIV-infected patients based on a population pharmacokinetic analysis.

Pharmacokinetic/pharmacodynamic relationship

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

PK/PD modelling using 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 and 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 and two or more secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with overall limited treatment options due to advanced multi-class resistance. There are no clinical data on the safety or efficacy of the 100 mg twice daily dose. Co-treatment with atazanavir increases the exposure of dolutegravir markedly, and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.

Special populations

Children

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 up to 18 years of age) found that a dose of dolutegravir 50 mg once daily resulted in Dolutegravir exposure comparable to that in adults who received a dose of 50 mg once daily. The pharmacokinetics in 11 children aged 6 to 12 years found that 25 mg once daily in patients weighing at least 20 kg and 35 mg once daily in patients weighing at least 30 kg resulted in dolutegravir exposure comparable to adults. In addition, population PK modelling and simulation analyses showed dosing on a weight-band basis (20, 25, 35, and 50 mg) in children of at least 6 years of age weighing at least 15 kg provides comparable exposure to those in adults (50 mg), with the lowest weight band of 15–20 kg corresponding to 20 mg daily.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in subjects aged over 65 years are limited.

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. Pharmacokinetics of dolutegravir were studied in adults with severe renal impairment (creatinine clearance less than 30 ml/minute) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 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 50 mg of dolutegravir 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

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

Race

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

Co-infection with Hepatitis B or C

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

5.3 Preclinical safety data

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

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

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption, reduced urine or feaces, suppressed bodyweight gain) was observed at 1000 mg/kg (0.40 times the 50 mg twice daily human clinical exposure based on AUC).

In a juvenile toxicity study in rats, dolutegravir administration resulted in two pre-weanling deaths at 75 mg/kg daily. Over the pre-weaning period, mean bodyweight gain was decreased and the decrease persisted throughout the entire 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, decreased bodyweight of the developing offspring was observed during lactation at a maternally toxic dose (about 27 times human exposure at the maximum recommended dose).

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

6. Pharmaceutical particulars

6.1 List of excipients

*Tablet Cor*e:

Mannitol, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate, Sodium Stearyl Fumarate.

Film-coating:

Poly Vinyl Alcohol, Macrogol 3350, Titanium dioxide, Talc, 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.

6.5 Nature and contents of container

HDPE container containing 30 tablets.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited,

India.

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