PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Ristegra Dispersible Tablets 10 mg dispersible tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 10 mg dolutegravir.

Contains sugar: mannitol (29,080 mg) per dispersible tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Dispersible tablet.

A pink coloured, film-coated, oval shape, biconvex tablet debossed with D on the left side and T on the right side of the score line on one side and M on the left side of the score line on other side. The tablet can be divided into two equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ristegra Dispersible Tablets is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral medicines in adults and children.

4.2 Posology and method of administration

Posology:

Ristegra Dispersible Tablets should be prescribed by medical practitioners experienced in the management of HIV infection.

Dolutegravir is also available as film-coated tablets. The bioavailability of film-coated tablets and dispersible tablets is not comparable therefore they must not be used as direct replacements (*see section 5.2*). For example, the recommended adult dose for film-coated tablets is 50 mg versus 30 mg for dispersible tablets. Patients changing between film-coated and dispersible tablets should follow the dosing recommendations that are specific for the formulation.

Ristegra Dispersible Tablets10 mg :

Adults:

Patients infected with HIV-1 without resistance to the integrase class:

The recommended dose of Ristegra Dispersible Tablets10 mg is 30 mg once daily.

Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected):

The recommended dose of Ristegra Dispersible Tablets10 mg is 30 mg twice daily. The decision to use Ristegra Dispersible Tablets10 mg for such patients should be informed by the integrase resistance pattern.

Adolescents, children and infants aged at least 4 weeks and weighing at least 3 kg:

Patients infected with HIV-1 without resistance to the integrase class:

The recommended dose of Ristegra Dispersible Tablets10 mg is determined according to weight and age and is presented in the table below.

Table 1a Dispersible tablet dose recommendations in adolescents, Children and infants aged at least 4 weeks and weighing at least 3 kg

Body Weight (kg)	**Dose**
3 to less than 6	5 mg once daily (taken as one half of a 10 mg dispersible tablets)
6 to less than 10	
< 6 months	10 mg once daily (taken as one 10 mg dispersible tablet)
≥ 6 months	15 mg once daily (taken as one and a half 10 mg dispersible tablets)
10 to less than 14	20 mg once daily (taken as two 10 mg dispersible tablets)
14 to less than 20	25 mg once daily (taken as two and a half 10 mg dispersible tablets)
20 or greater	30 mg once daily (taken as three 10 mg dispersible tablets)

***Dispersible tablet dose recommendations in adolescents, children and infants aged at least 4 weeks and weighing at least 3 kg*:**

There are insufficient safety and efficacy data available to recommend a dose for Ristegra Dispersible Tablets10 mg in children below age 4 weeks or weighing less than 3 kg.

Patients infected with HIV-1 with resistance to the integrase class:

There are insufficient data to recommend a dose for Ristegra Dispersible Tablets10 mg in integrase inhibitor resistant adolescents, children and infants.

Missed doses: If the patient misses a dose of Ristegra Dispersible Tablets, the patient should take Ristegra Dispersible Tabletsas soon as possible, providing 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 simply resume the usual dosing schedule.

Special populations:

Elderly:

There are limited data available on the use of Ristegra Dispersible Tablets10 mg in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (*see section 5.2 Special Patient Populations*).

Renal impairment:

No dosage adjustment is required in patients with mild, moderate or severe (CrCl < 30 ml/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis, although differences in pharmacokinetics are not expected in this population (*see section 5.2 Special Patient Populations*).

Treatment with Ristegra Dispersible Tabletsresulted in an early small increase of mean serum creatinine levels by 10-14 % which remained stable over time and is not considered clinically relevant *(see section 4.8)*.

Hepatic impairment:

No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh grade A or B). Ristegra Dispersible Tablets10 mg is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) *(see section 4.3*).

Method of administration:

Dispersible tablets:

Ristegra Dispersible Tabletscan be taken with or without food.

The dispersible tablets may be swallowed whole with drinking water or dispersed in drinking water. When dispersed, the amount of water will depend on the number of tablets prescribed. The tablet should not be chewed cut or crushed.

4.3 Contraindications

- Ristegra Dispersible Tablets is contraindicated in patients with known hypersensitivity to dolutegravir or to any of the excipients of Ristegra Dispersible Tablets(*see section 6.1*).
- Ristegra Dispersible Tablets is contraindicated in combination with dofetilide and pilsicainide.
- Ristegra Dispersible Tablets is contraindicated in severe hepatic impairment

(Child-Pugh grade C).

Ristegra Dispersible Tabletsis contraindicated in the first trimester of pregnancy (*see section 4.6.)*

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including Ristegra Dispersible Tablets and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue Ristegra Dispersible Tablets and other suspect medicines immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with Ristegra Dispersible Tablets or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and elevated serum lipid and glucose levels in HIV (+) patients. Clinical examination

should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Syndrome:

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal atypical mycobacterial infections and *Pneumocystis jiroveci* pneumonia (PJP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of TIVICAY therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients *(see section 4.8)*.

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, high body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Hepatic impairment:

The unbound fraction of dolutegravir in the blood is doubled in patients with moderate hepatic impairment. Ristegra Dispersible Tabletsis contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh grade C) (*see section 4.3*). The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir have not been studied.

Interactions:

Caution should be given to co-administering medicines (prescription and non-prescription) that may change the exposure of Ristegra Dispersible Tablets or medicines that may have their exposure changed by Ristegra Dispersible Tablets (*see sections 4.3 and section 4.5*).

The recommended adult dose of Ristegra Dispersible Tablets should be given twice daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, tipranavir/ritonavir, rifampicin, carbamazepine,

phenytoin, phenobarbitone and St. John's wort (*see section 4.5*). In paediatric patients, the weight-based once daily dose should be administered twice daily. Ristegra Dispersible Tablets should not be co-administered with polyvalent cation-containing antacids. Ristegra Dispersible Tablets is recommended to be administered 2 hours before or 6 hours after these medicines *(see section 4.5*). Ristegra Dispersible Tablets is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered after food.

Ristegra Dispersible Tablets increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of Ristegra Dispersible Tabletswith metformin, to maintain glycaemic control.

Co-infection with Hepatitis B or C:

In Phase III studies, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of Ristegra Dispersible Tablets therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Opportunistic infections:

Patients receiving Ristegra Dispersible Tablets or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases.

Transmission of infection:

Patients should be advised that current antiretroviral therapy, including Ristegra Dispersible Tablets, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

4.5 Interaction with other medicines and other forms of interaction

Effect of Ristegra Dispersible Tablets on the pharmacokinetics of other medicines:

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 Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, Ristegra Dispersible Tablets is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or

transporters (e.g., reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals (such as fluconazole, itraconazole, clotrimazole), proton pump inhibitors (such as esomeprazole, lansoprazole, omeprazole), anti-erectile dysfunction medicines (such as sildenafil, tadalafil, vardenafil), acyclovir, valacyclovir, sitagliptin, adefovir).

In medicine interaction studies, dolutegravir, as contained in Ristegra Dispersible Tablets did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, boceprevir, telaprevir, daclatasvir and oral contraceptives containing norgestimate and ethinyl oestradiol.

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) (IC50 = 1.93 µM), multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 6,34 µM) and MATE2-K (IC50 = 24,8 µM). Given dolutegravir's in vivo exposure, it has a low potential to affect the transport of MATE2-K substrates *in vivo*). *In vivo* Ristegra Dispersible Tablets may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, pilsicainide or metformin) (see Table 2: Medicine Interactions – Other medicines).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC50 = 2,12 µM) and OAT3 (IC50 = 1,97 µM). However, dolutegravir had no notable effect on the *in vivo* pharmacokinetics of the OAT substrates tenofovir and para aminohippurate and therefore has low propensity to cause interactions via inhibition of OAT transporters.

Effect of Other Medicines on the Pharmacokinetics of Ristegra Dispersible Tablets:

Ristegra Dispersible Tablets is eliminated mainly through metabolism by UGT1A1. Ristegra Dispersible Tablets is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore, medicines that induce those enzymes may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of Ristegra Dispersible Tablets.

Co-administration of Ristegra Dispersible Tablets and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 2).

In vitro, dolutegravir is not a substrate of human organic anion transporting polypeptide (OATP)1B1, OATP1B3, or OCT1, therefore medicines that solely modulate these transporters are not expected to affect dolutegravir plasma concentration.

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require Ristegra Dispersible Tablets dose adjustment to the recommended dose twice daily.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in Ristegra Dispersible Tablets.

Etravirine also reduced plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir.

Therefore, no Ristegra Dispersible Tablets dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of Ristegra Dispersible Tablets. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 2: Medicine Interactions – HIV-1 Antiviral Medicines). A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no Ristegra Dispersible Tablets dose adjustment is required when co-administered with these medicines.

Table 2: Medicine Interactions

Concomitant Medicine Class: Medicine Name	**Effect on Concentra of Ristegra Dispersible Tablets or Concomitant Medicine**	**Clinical Comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR) without boosted protease inhibitor	Dolutegravir ↓ AUC ↓ 71 % C_{max}↓ 52 % C_T ↓ 88 % ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of Ristegra Dispersible Tablets should be given twice daily when co-administered with etravirine without boosted protease inhibitors. Ristegra Dispersible Tablets should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients.

Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑ 11 % C_{max} ↑ 7 % C_T ↑ 28 % LPV↔ RTV ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % C_T ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Ristegra Dispersible Tablets or Concomitant Medicine**	**Clinical Comment**
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC↓ 57 % C_{max} ↓ 39 % C_T↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of Ristegra Dispersible Tablets should be given twice daily when co- administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of Ristegra Dispersible Tablets should be given twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.

Protease Inhibitor (PI): Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max}↑ 50 % C_T↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max}↑ 33 % C_T ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Ristegra Dispersible Tablets or Concomitant Medicine**	**Clinical Comment**
Protease Inhibitor: Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % C_T ↓ 76 % ATV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of Ristegra Dispersible Tablets should be given twice daily when co- administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Fosamprenavir/ ritonavi (FPV+RTV)	Dolutegravir ↓ AUC↓ 35 % C_{max} ↓ 24 % C_T ↓ 49 % FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INI resistant patients.

Protease Inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV+RTV)	DTG ↔ AUC ↓ 4 % Cmax ↔ 6 % LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Ristegra Dispersible Tablets or Concomitant Medicine**	**Clinical Comment**
Protease Inhibitor: Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 22 % C_{max} ↓ 11 % C_T↓ 38 % DRV ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDV)	Dolutegravir ↔ AUC ↔ C_{max} ↓ 3 % C_T ↓ 8 % TDV ↔ AUC ↑ 12 % C_{max} ↑ 9 % C_T↑ 19 %	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % C_T ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Other Medicines		
Concomitant Medicine Class: Medicine Name	**Effect on Concentration of [PRODCUT NAME] or Concomitant Medicine**	**Clinical Comment**
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with Ristegra Dispersible Tablets is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Carbamazepine	Dolutegravir↓ AUC ↓ 49 % Cmax ↓ 33 % C_T ↓ 73 %	Carbamazepine decreased dolutegravir plasma concentration. The recommended dose of Ristegra Dispersible Tablets should be given twice daily when co- administered with carbamazepine. Alternatives to carbamazepine should be used where possible for INI resistant patients.

Phenytoin Phenobarbitone St. John's wort	Dolutegravir↓	Co-administration with these metabolic inducers has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of these metabolic inducers on dolutegravir exposure is likely similar to carbamazepine. The recommended dose of Ristegra Dispersible Tabletsshould be given is twice daily when co- administered with these metabolic inducers. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Oxcarbazepine	Dolutegravir ↓	This interaction has not been studied. Although an inducer of CYP3A4, based on data from other inducers, a clinically significant decrease in dolutegravir is not expected. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Ristegra Dispersible Tablets or Concomitant Medicine**	**Clinical Comment**
Antacids containing polyvalent cations (e.g., Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. Ristegra Dispersible Tablets is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	Ristegra Dispersible Tablets is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administer with food.

Iron supplements	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 57 % C_{24} ↓ 56 %	Ristegra Dispersible Tablets is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Ristegra Dispersible Tablets or Concomitant Medicine**	**Clinical Comment**
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg film coated tablets QD (four times per day) Metformin AUC↑ 79 % C_{max} ↑ 66 % When co-administered with dolutegravir 50 mg BD (twice daily) Metformin AUC↑ 145 % C_{max}↑ 111 %	Co-administration of dolutegravir increased metformin plasma concentration. A dose adjustment of metformin should be considered when starting and stopping co-administration of Ristegra Dispersible Tabletswith metformin, to maintain glycaemic control.
Rifampicin	Dolutegravir↓ AUC ↓ 54 %	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of Ristegra Dispersible Tabletsshould be

	C_{max} ↓ 43 % C_T ↓ 72 %	given twice daily when co- administered with rifampicin. Alternatives to rifampicin should be used where possible for INI resistant patients.

Concomitant Medicine Class: Medicine Name	**Effect on Concentra of Ristegra Dispersible Tablets or Concomitant Medicine**	**Clinical Comment**
Oral contraceptives (Ethinyl estradiol (EE) a Norgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max}↓ 1 % C_T ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC↓ 2 % C_{max} ↓ 11 % C_T ↓ 7 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with Ristegra Dispersible Tablets.
Methadone	Effect of dolutegravir: Methadone↔ AUC↓ 2 % C_{max} ↔ 0 % C_T ↓ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with Ristegra Dispersible Tablets.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33 % C_{max} ↑ 29 % C_T ↑ 45 % Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.

Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max}= maximum observed concentration, C_T = concentration at the end of dosing interval.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females:

Women of childbearing potential should be counseled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of Ristegra Dispersible Tablets in women of childbearing potential to exclude inadvertent (unintentional) use of Ristegra Dispersible Tablets during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with dolutegravir versus using another antiretroviral regimen should be discussed with her.

Pregnancy:

Use of dolutegravir at the time of conception was associated with a small increase in the prevalence of neural tube defects (0,19%) compared to non-dolutegravir regimens (0,11%). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral

regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.
Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus. Dolutegravir was shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

Breastfeeding:

HIV infected women should not breast-feed their infants in order to avoid transmission of HIV or follow appropriate guidelines. Dolutegravir is excreted in human breast milk in small amounts. There is insufficient information on the effects of dolutegravir in neonates/infants.

Fertility:

There are no data on the effects of dolutegravir 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

Ristegra Dispersible Tablets may cause dizziness. The clinical status of the patient and the adverse event profile of Ristegra Dispersible Tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Adverse drug reactions (ADRs) are listed below by system organ class and by frequency.

Tabulated summary of adverse reactions (Table 3)

Immune system disorders	Less frequent	Hypersensitivity *(see section 4.4)* Immune Reconstitution Syndrome *(see section 4.4)*
Psychiatric disorders	Frequent	Insomnia Abnormal dreams Depression Anxiety
	Less frequent	Suicide ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness
Nervous system disorders	Frequent	Headache Dizziness
Gastrointestinal disorders	Frequent	Nausea Diarrhoea Vomiting Flatulence Upper abdominal pain
	Less frequent	Abdominal pain Abdominal discomfort
Hepatobiliary disorders	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash Pruritus
General disorders and administration site conditions	Frequent	Fatigue

The safety profile was similar across the treatment naïve, treatment experienced (and integrase naïve) and integrase resistant patient populations.

Post-marketing data:

Hepatobiliary disorders: acute hepatic failure (acute hepatic failure has been reported in a dolutegravir-containing regimen. The contribution of dolutegravir in these cases is unclear).

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

Investigations: weight increased.

Description of selected adverse reactions

Changes in laboratory chemistries:

Increases in serum creatinine occurred within the first week of treatment with Ristegra Dispersible Tablets and remained stable through 48 weeks. In treatment naïve patients a mean change from baseline of 9,96 µmol/ℓ (range: -53 µmol/ℓ to 54,8 µmol/ℓ) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment experienced patients. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (*see section 5.1 Effects on Renal Function and section 4.2 Posology, Special populations*).

Small increases in total bilirubin (without clinical jaundice) may occur on Ristegra Dispersible Tablets and raltegravir (but not efavirenz) arms in the programme. These changes are not considered clinically relevant as they likely reflect

competition between Ristegra Dispersible Tablets and unconjugated bilirubin for a common clearance pathway (UGT1A1) *(see section 5.2 Biotransformation*). Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with Ristegra Dispersible Tablets therapy.

Paediatric population:

Based on limited available data in children and adolescents (6 to less than 18 years of age), 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/wp-ontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

Management should be as clinically indicated or as recommended by the national poisons centre, where available.

There is no specific treatment for an overdose of Ristegra Dispersible Tablets. If overdose occurs, the patient should be treated supportively with appropriate

monitoring as necessary. As Ristegra Dispersible Tablets is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemis use, other antivirals, ATC code: J05AX12;

Pharmacological classification: A 20.2.8 Antiviral agents

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. In vitro, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t ½ 71 hours).

Resistance *in vitro*:

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir were not observed during HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir integrase substitutions observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wildtype subtype B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

Integrase Inhibitor-Resistant HIV-1 Strains: Dolutegravir showed anti-HIV activity (susceptibility) with FC < 5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R and N155H.

Integrase Inhibitor-Resistant HIV-2 Strains: Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall, the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Clinical Isolates From Raltegravir Treatment Virologic Failure Subjects:
Seven hundred and five raltegravir resistant clinical isolates were analysed for susceptibility to dolutegravir using the Monogram Biosciences PhenoSense assay. Dolutegravir has a < 10 FC against 93,9 % of the 705 clinical isolates.

Resistance in vivo: integrase inhibitor naïve patients:

No integrase inhibitor (INI)-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg film coated tablets once daily in treatment-naïve studies (SPRING-1, SPRING-2 and SINGLE studies). In the SAILING study for treatment experienced (and integrase naïve) patients (n = 354 in the dolutegravir arm), treatment emergent integrase resistance was observed in 2 of 9 subjects with virologic failure. In both cases, a unique R263K integrase substitution was observed, with a maximum FC of 1,93.

Resistance *in vivo*: integrase inhibitor resistant patients:

The VIKING-3 study examined dolutegravir (plus optimised background therapy) in subjects with pre-existing INI resistance. Twenty-six subjects (26/114) experienced protocol defined virologic failure through to Week 24. Of these, 25 had paired baseline and PDVF resistance data for analysis and 13/25 (52 %) had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were E92Q (n = 2), T97A (n = 6), E138K/A (n = 4), G140S (n=2), Y143H (n = 1), S147G (n=1), Q148H/K/R (n = 3), and N155H (n = 1). Eleven of the 13 subjects with virus exhibiting treatment-emergent mutations harboured Q148 pathway virus present at baseline or historically.

Paediatric population:

In a study, the pharmacokinetic parameters, safety, tolerability and efficacy of a dolutegravir formulation was evaluated in combination regimens in HIV-1 infected infants, children and adolescents (12 to less than 18 years of age).

Table 4 Virologic and Immunologic Activity of Treatment for Subjects 6 Years and Older in study P1093

	Dolutegravir ~1 mg/kg Once Daily + OBR	
	Cohort I (12 to 18 years) Week 48 (n=23)	Cohort IIa (6 to <12 years) Week 24 (n=23)

HIV-1 RNA <50 copies/ml, n (%)	14 (61 %)	14 (61 %)
HIV-1 RNA <400 copies/ml, n (%)	17 (74 %)	19 (83 %)
Virologic non response	6	3
CD4+ Cell Count		
Median Change from Baseline, cells/mm^3	84[a]	209[b]
Median Percent Change from Baseline	5 %[a]	8% [b]

a 22 subjects contributed Week 48 CD4+ cell count data

b 21 subjects contributed Week 24 CD4+ cell count data

Effects on Renal Function:

The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomised, 3 arm, parallel, placebo-controlled study in 37 healthy subjects, who were administered dolutegravir film-coated tablets 50 mg once daily (n = 12), 50 mg twice daily (n = 13) or placebo once daily (n = 12) for 14 days. A small decrease of 10-14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on glomerular filtration rate (GFR) or the effective renal plasm flow (ERPF). *In vitro* studies suggest that the increases in creatinine observed in clinical studies are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

5.2 Pharmacokinetic properties

Dolutegravir pharmacokinetic parameters are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy subjects, between-subject CVb % for AUC and C_{max} ranged from ~20 to 40 % and Cт from 30 to 65 % across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw %) is lower than between-subject variability.

The relative bioavailability of dispersible tablets is approximately 1,6-fold higher as compared to film-coated tablets. Thus, a 30 mg dolutegravir dose administered as three 10 mg dispersible tablets will have similar exposure to a 50 mg DTG dose administered as film-coated tablet(s).

Absorption

Dolutegravir is absorbed following oral administration with a median T_{max} at 2 to 3 hours post dose for the tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however, increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. 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 34 %, 41 %, and 66 %, increased C_{max} by 46 %, 52 %, and 67 %, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.
The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on in vitro data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12,5 ℓ. Binding of dolutegravir to plasma proteins was independent of 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. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects, approximately 0,4 to 0,5 % in subjects with moderate hepatic impairment, and 0,8 to 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients.
Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/ml (comparable to unbound plasma concentration, and above the IC50); CSF:plasma concentration ratio of dolutegravir ranged from 0,11 to 0,66 %. Dolutegravir concentrations in CSF exceeded the IC50, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy *(section 5.1)*.

Biotransformation

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose).

Elimination

Dolutegravir has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 0,56 ℓ/hr.

Special patient populations

Paediatric population

The pharmacokinetics of dolutegravir film-coated and dispersible tablets in HIV-1 infected infants, children and adolescents aged ≥ 4 weeks to < 18 years were evaluated in two on-going studies (P1093/ING112578 and ODYSSEY/201296). Steady state plasma exposure at weight band doses are summarized in Table 5.

Table 5 Summary of DTG PK Parameters following Administration of DTG at Weight Band Doses in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	Ristegra Dispersible Tablets Dosage Form	Once Daily Dose (mg)	N	PK Parameter Geometric Mean (%CV)		
				Cmax (µg/mL)	AUC0-24h (µg*h/mL)	C24h (ng/mL)
3 to <6	DT	5	8	3.80 (34)	49.37 (49)	962 (98)
6 to <10[b]	DT	10	4	5.68 (38)	85.49 (32)	1821 (41)
6 to <10[c]	DT	15	17	5.27 (50)	57.17 (76)	706 (177)
10 to <14	DT	20	13	5.99 (33)	68.75 (48)	977 (100)
14 to <20	DT	25	19	5.97 (42)	58.97 (44)	725 (75)
≥20	DT[d]	30	9	7.16 (26)	71.53 (26)	759 (73)
	FCT	50	49	4.92 (40)	54.98 (43)	778 (62)
Target: Geometric Mean (range)					**46 (37-134)**	**995 (697-2260)**

DT=dispersible tablet

FCT=film-coated tablet

- The bioavailability of *Ristegra Dispersible Tablets* is ~1.6-fold *Ristegra Dispersible Tablets* FCT.
- < 6 months of age
- ≥ 6 months of age

- ≥ 20 to < 25 kg weight band

Elderly

Pharmacokinetic data for dolutegravir in subjects of > 65 years old are limited.

Renal impairment

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of a single 50 mg dose of dolutegravir film coated tablets was performed in subjects with severe renal impairment (CLcr < 30 ml/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 ml/min) and matching healthy subjects were observed, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 %, and 43 %, respectively, compared with those in matched healthy subjects. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. No dosage adjustment is necessary for patients with mild hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in metabolising enzymes

There is no evidence that common polymorphisms in metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Calcium sulfate

Crospovidone

Mannitol (E421)

Microcrystalline cellulose

Povidone

Silicified microcrystalline cellulose

Sodium starch glycolate

Sodium stearyl fumarate

Strawberry cream flavour

Sucralose

Film Coat:

Black iron oxide (E172)

Hypromellose

Polyethylene glycol

Red iron oxide (E172)

Titanium dioxide (E171)

Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original container.

Keep the bottle tightly closed and protected from moisture.

6.5 Nature and contents of container

Available in HDPE Bottle pack of 30’s, 60’s, 90’s,180’s and 270’s*

* Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MYLAN (PTY) LTD

4 Brewery street

Isando

Gauteng

Republic of South Africa

8 REGISTRATION NUMBERS

MASTER: Odinsti Dispersible Tablets: 56/20.2.8/0018

DUPLICATE: Ristegra Dispersible Tablets: 56/20.2.8/0019.018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/06/2022

10 DATE OF REVISION OF THE TEXT