PROFESSIONAL INFORMATION FOR SYROMAK 10 ODT

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SYROMAK 10 ODT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SYROMAK 10 ODT

Each **SYROMAK 10 ODT** 10 mg film-coated, dispersible tablet for oral suspension contains dolutegravir sodium 10.52 mg equivalent to dolutegravir 10 mg.

Contains sweetener (29.08 mg of mannitol and 1.20 mg of sucralose).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated, dispersible tablets for oral suspension.

SYROMAK 10 ODT:

Pink colored, caplet shaped; film coated tablets, debossed “K” and “1” separated by breakline on one side and breakline on other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SYROMAK 10 ODT 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

SYROMAK 10 ODT therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

DOLUTEGRAVIR SODIUM TABLET is available as film-coated tablets for patients aged at least 6 years and weighing at least 14 kg. **DOLUTEGRAVIR SODIUM TABLET** is also available as dispersible tablets for patients aged at least 4 weeks and weighing at least 3 kg or for patients in whom film-coated tablets are not appropriate. 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 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.

Adults:

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

The recommended dose of dolutegravir dispersible tablets is 30 mg once daily.

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

The recommended dose of dolutegravir dispersible tablets is 30 mg twice daily. The decision to use dolutegravir 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 dolutegravir dispersible tablets is determined according to weight and age and is presented in the table below.

Table 1 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 half a 10 mg dispersible tablet daily)
6 to less than 10 < 6 months ≥ 6 months	 10 mg once daily 15 mg once daily (Taken as one and a half 10 mg dispersible tablet daily)
10 to less than 14	20 mg once daily (Taken as two 10 mg dispersible tablets daily)
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 dolutegravir dispersible tablets 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 dolutegravir in integrase inhibitor resistant adolescents, children and infants.

To reduce the risk of choking, do not swallow more than one tablet at a time, and where possible, children weighing 14 to less than 20 kg should preferentially take the dispersible tablet formulation.

Missed doses:

If the patient misses a dose of **SYROMAK 10 ODT**, the patient should take **SYROMAK 10 ODT** as 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 **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT** resulted 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). **SYROMAK 10 ODT** is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) (see section 4.3).

Method of administration

For oral use

SYROMAK 10 ODT can 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 no be chewed, cut or crushed.

4.3 Contraindications

- **SYROMAK 10 ODT** is contraindicated in patients with known hypersensitivity to dolutegravir or to any of the excipients listed in section 6.1.
- **SYROMAK 10 ODT** is contraindicated in combination with dofetilide and pilsicainide.
- **SYROMAK 10 ODT** is contraindicated in severe hepatic impairment (Child-Pugh grade C).
- **SYROMAK 10 ODT** is contraindicated in the first trimester of pregnancy (see Section 4.6).
- **SYROMAK 10 ODT** must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including but not limited to fampridine (also known as dalfampridine; see section 4.5).

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Integrase class resistance of particular concern:

The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring Q148+≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I (see section 5.1). To what extent dolutegravir provides added efficacy in the presence of such integrase class resistance is uncertain (see section 5.2).

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including **SYROMAK 10 ODT** and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT** 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. **SYROMAK 10 ODT** is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh grade C) (see section 4.3). The effects 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 **SYROMAK 10 ODT** or medicines that may have their exposure changed by **SYROMAK 10 ODT** (see sections 4.3 and section 4.5).

The recommended adult dose of **SYROMAK 10 ODT** is 50 mg 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.

SYROMAK 10 ODT should not be co-administered with polyvalent cation-containing antacids. **SYROMAK 10 ODT** is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).

SYROMAK 10 ODT is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered after food.

SYROMAK 10 ODT increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of **SYROMAK 10 ODT** with metformin, to maintain glycaemic control.

Co-infection with Hepatitis B or C:

In 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 **SYROMAK 10 ODT** therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Opportunistic infections:

Patients receiving **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT**, 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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Excipients

This medicine contains less than 1 mmol sodium (23mg) per tablet that is to say is essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

Effect of SYROMAK 10 ODT on the Pharmacokinetics of Other Medicines:

In vitro, **SYROMAK 10 ODT** 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, **SYROMAK 10 ODT** 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, **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT** may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, pilsicainide or metformin) (see Table 4: 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 SYROMAK 10 ODT:

SYROMAK 10 ODT is eliminated mainly through metabolism by UGT1A1. **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT.**

Co-administration of **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT** dose adjustment to 50 mg twice daily.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in **SYROMAK 10 ODT**.

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 **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT.** 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 **SYROMAK 10 ODT** dose adjustment is required when co-administered with these medicines.

Table 2: Medicine Interactions

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of SYROMAK 10 ODT or Concomitant Medicine**	**Clinical Comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR) without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % Cτ ↓ 88 % ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended adult dose of **SYROMAK 10 ODT** is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. In paediatric patients the weight-based once daily dose should be administered twice daily. **SYROMAK 10 ODT** 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 % Cτ ↑ 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 % Cτ ↓ 36 % DRV ↔ RTV ↔	Darunavir/ ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39 % Cτ ↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended adult dose of **SYROMAK 10 ODT** is 50 mg twice daily when co-administered with efavirenz. In paediatric patients the weight-based once daily dose should be administered twice daily. 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 adult dose of **SYROMAK 10 ODT** is 50 mg twice daily when co-administered with nevirapine. In paediatric patients the weight-based once daily dose should be administered twice daily. 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 % Cτ ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % Cτ ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % Cτ ↓ 76 % TPV ↔ RTV ↔	Tipranavir/ ritonavir decreases dolutegravir concentrations. The recommended adult dose of **SYROMAK 10 ODT** is 50 mg twice daily when co-administered with tipranavir/ ritonavir. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include tipranavir/ ritonavir should be used where possible in INI resistant patients.

Protease Inhibitor: Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % Cτ ↓ 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 % C_{max} ↔ ↓ 6 % LPV ↔ RTV ↔	Lopinavir/ ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 22 % C_{max} ↓ 11 % Cτ ↓ 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:	Dolutegravir ↔ AUC ↔ C_{max} ↓3 %	Tenofovir did not change dolutegravir plasma concentration to a clinically

Tenofovir (TDV)	$C\tau \downarrow$ 8 % TDV $\leftrightarrow$ AUC $\uparrow$ 12 % $C_{max} \uparrow$ 9 % $C\tau \uparrow$ 19 %	relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir $\downarrow$ AUC $\downarrow$ 25 % $C_{max} \downarrow$ 12 % $C\tau \downarrow$ 36 % DRV $\leftrightarrow$ RTV $\leftrightarrow$	Darunavir/ ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Medicines		
Dofetilide Pilsicainide	Dofetilide $\uparrow$ Pilsicainide $\uparrow$	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 **SYROMAK 10 ODT** is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Carbamazepine	Dolutegravir $\downarrow$ AUC $\downarrow$ 49 % Cmax $\downarrow$ 33 % $C\tau \downarrow$ 73 %	Carbamazepine decreased dolutegravir plasma concentration. The recommended adult dose of **SYROMAK 10 ODT** is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients the

		weight-based once daily dose should be administered twice daily. 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 adult dose of **SYROMAK 10 ODT** is 50 mg twice daily when co-administered with these metabolic inducers. In paediatric patients the weight-based once daily dose should be administered twice daily. 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.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. **SYROMAK 10 ODT** 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 %	**SYROMAK 10 ODT** 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 %	**SYROMAK 10 ODT** is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑ When co-administered with **SYROMAK 10 ODT** QD (four times per day) Metformin AUC ↑ 79 % C_{max} ↑ 66 % When co-administered with **SYROMAK 10 ODT** BID (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 **SYROMAK 10 ODT** with metformin, to maintain glycaemic control.

Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % Cτ ↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. The recommended adult dose of **SYROMAK 10 ODT** is 50 mg twice daily when co-administered with rifampicin. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternatives to rifampicin should be used where possible for INI resistant patients.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % Cτ ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % Cτ ↓ 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 **SYROMAK 10 ODT.**
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % Cτ ↓ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with **SYROMAK 10 ODT**.

Daclatasvir	Dolutegravir ↔ AUC ↑ 33 % C_{max} ↑ 29 % Cτ ↑ 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, Cτ= concentration at the end of dosing interval.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be counselled 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 **SYROMAK 10 ODT** in women of childbearing potential to exclude inadvertent (unintentional) use of **SYROMAK 10 ODT** 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

Breast-feeding

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

Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the reported safety profile

The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4). The most frequently seen treatment emergent adverse reactions were nausea, diarrhoea and headache.

Table 3 Tabulated summary of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Immune system disorders	-	Hypersensitivity (see section 4.4), Immune Reconstitution Syndrome (see section 4.4)	-
Psychiatric disorders	Insomnia, abnormal dreams, depression, anxiety	Suicide ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness	-
Nervous system disorders	Headache, dizziness	-	-

Gastrointestinal disorders	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain	Abdominal pain, abdominal discomfort,	-

Hepatobiliary disorders	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations	Hepatitis, acute hepatic failure, increased bilirubin*	-

Skin and subcutaneous tissue disorders	Rash, pruritus	-	-

Musculoskeletal and connective tissue disorders	-	Arthralgia, myalgia	-

General disorders and administration site conditions	Fatigue	-	-

Investigations	Creatine phosphokinase (CPK) elevations	-	Weight increased.

*****In combination with increased transaminases.

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

Description of selected adverse reactions

Changes in laboratory chemistries:

Increases in serum creatinine occurred within the first week of treatment with **SYROMAK 10 ODT** 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).

Small increases in total bilirubin (without clinical jaundice) were observed on **SYROMAK 10 ODT** and raltegravir (but not efavirenz) arms in the programme. These changes are not considered clinically relevant as they likely reflect competition between **SYROMAK 10 ODT** 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 **SYROMAK 10 ODT** therapy.

Co-infection with Hepatitis B or C

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 dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section 4.4).

Immune reactivation syndrome

In HIV-infected 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 and autoimmune hepatitis) 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).

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Paediatric population:

Based on limited available data from studies in infants, children and adolescents (aged 4 weeks and above, to less than 18 years, and weighing at least 3 kg), who received the recommended doses of dispersible tablets or film-coated tablets once daily, 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 Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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 **SYROMAK 10 ODT**. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As **SYROMAK 10 ODT** is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.8 Antiviral agents

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. *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 analyzed 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 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 clinical studies, the pharmacokinetic parameters, safety, tolerability and efficacy of dolutegravir was evaluated in combination regimens in HIV-1 infected infants, children and adolescents.

At 48 weeks, 14 of 23 (61 %) children and adolescents (12 to less than 18 years of age) treated with dolutegravir once daily (35 mg n = 4, 50 mg n = 19) plus OBR achieved viral load less than 50 copies/mL.

At 24 weeks, 14 of 23 (61 %) children (6 to less than 12 years of age) treated with dolutegravir (70 mg, as 35 mg twice daily, n = 1; 50 mg once daily, n = 5; 35 mg once daily, n = 6; 25 mg once daily, n = 8; and 20 mg once daily, n = 3) plus OBR, achieved viral load less than 50 copies/mL.

Table 4 Virologic and Immunologic Activity of Treatment for Subjects 6 Years and Older in 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 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 non pathologic 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 pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. In Phase I studies in healthy subjects, between-subject CVb % for AUC and C_{max} ranged from ~20 to 40 % and $C\tau$ 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.

Dispersible tablets and film-coated tablets do not have the same bioavailability. 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 dolutegravir dose administered as film-coated tablet(s). Similarly, a 25 mg dolutegravir dose administered as two and a half 10 mg dispersible tablets will provide comparable exposure to a 40 mg dolutegravir dose administered as four 10 mg film-coated tablets.

Absorption:

Dolutegravir is absorbed following oral administration, with 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.

Linearity/non-linearity

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of film-coated tablet formulations, in general, 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 for the film-coated tablet formulation. With 50 mg film-coated tablet twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg film-coated tablet once daily.

Special patient populations:

Paediatric population:

The pharmacokinetics of dolutegravir given once daily as dispersible and film-coated tablets in HIV-1 infected infants, children and adolescents aged ≥ 4 weeks to < 18 years were evaluated in two on-going studies Steady state simulated plasma exposure at once daily weight band doses is summarized in Table 5.

Table 5 Summary of Simulated Dolutegravir PK Parameters at Once Daily Doses by Weight Band in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	**Dolutegravir Dosage Form[a]**	**Once Daily Dose (mg)**	**PK Parameter Geometric Mean (90% CI)**		
			C_{max} (µg/mL)	**AUC0-24h (µg*h/mL)**	**C24h (ng/mL)**
3 to <6	DT	5	4.02 (2.12, 7.96)	49.4 (21.6, 115)	1070 (247, 3830)
6 to <10[b]	DT	10	5.90 (3.23, 10.9)	67.4 (30.4, 151)	1240 (257, 4580)

6 to <10[c]	DT	15	6.67 (3.75, 12.1)	68.4 (30.6, 154)	964 (158, 4150)
10 to <14	DT	20	6.61 (3.80, 11.5)	63.1 (28.9, 136)	719 (102, 3340)
14 to <20	DT FCT	25 40	7.17 (4.10, 12.6) 6.96 (3.83, 12.5)	69.5 (32.1, 151) 72.6 (33.7, 156)	824 (122, 3780) 972 (150, 4260)
20 to <25	DT FCT	30 50	7.37 (4.24, 12.9) 7.43 (4.13, 13.3)	72.0 (33.3, 156) 78.6 (36.8, 171)	881 (137, 3960) 1080 (178, 4690)
25 to <30	FCT	50	6.74 (3.73, 12.1)	71.4 (33.2, 154)	997 (162, 4250)
30 to <35	FCT	50	6.20 (3.45, 11.1)	66.6 (30.5, 141)	944 (154, 4020)
≥35	FCT	50	4.93 (2.66, 9.08)	54.0 (24.4, 118)	814 (142, 3310)
Target: Geometric Mean				46 (37-134)	995 (697-2260)

DT=dispersible tablet

FCT=film-coated tablet

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

a. < 6 months of age

b. ≥ 6 months of age

Steady state simulated plasma exposure at alternative twice daily weight band doses is summarized in Table 6. In contrast to once daily dosing, simulated data for alternative twice daily dosing have not been confirmed in clinical trials.

Table 6 Summary of Simulated Dolutegravir PK Parameters at Alternative Twice Daily Doses by Weight Band in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	**Dolutegravir Dosage Form[a]**	**Twice Daily Dose (mg)**	**PK Parameter Geometric Mean (90% CI)**		
			C_{max} (µg/mL)	**AUC0-12h (µg*h/mL)**	**C12h (ng/mL)**
6 to <10[b]	DT	5	4.28 (2.10, 9.01)	31.6 (14.6, 71.4)	1760 (509, 5330)
6 to <10[c]	DT	10	6.19 (3.15, 12.6)	43.6 (19.4, 96.9)	2190 (565, 6960)
10 to <14	DT	10	4.40 (2.27, 8.68)	30.0 (13.5, 66.0)	1400 (351, 4480)
14 to <20	DT	15	5.78 (2.97, 11.4)	39.6 (17.6, 86.3)	1890 (482, 6070)
	FCT	20	4.98 (2.55, 9.96)	35.9 (16.5, 77.4)	1840 (496, 5650)
20 to <25	DT	15	5.01 (2.61, 9.99)	34.7 (15.8, 76.5)	1690 (455, 5360)

	FCT	25	5.38 (2.73, 10.8)	39.2 (18.1, 85.4)	2040 (567, 6250)
25 to <30	DT FCT	15 25	4.57 (2.37, 9.05) 4.93 (2.50, 9.85)	32.0 (14.6, 69.1) 35.9 (16.4, 77.4)	1580 (414, 4930) 1910 (530, 5760)
30 to <35	FCT	25	4.54 (2.31, 9.10)	33.3 (15.3, 72.4)	1770 (494, 5400)
≥35	FCT	25	3.59 (1.76, 7.36)	26.8 (12.1, 58.3)	1470 (425, 4400)

DT=dispersible tablet

FCT=film-coated tablet

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

a. <6 months of age

b. ≥6 months of age

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure. Pharmacokinetic data for dolutegravir in subjects > 65 years of age are limited.

Renal impairment

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir 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. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. 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. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32 % lower clearance of dolutegravir and 46 % higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41). 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 contains:

Calcium sulphate dihydrate, crospovidone, mannitol, microcrystalline cellulose, povidone, silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, strawberry cream flavor, sucralose

Coating material contains:

Hypromellose, titanium dioxide, macrogol, iron oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the manufacturing date

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original package to protect from moisture.

Keep the HDPE container tightly closed.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

HDPE container pack:

Tablets are packed in a round white HDPE container closed with child resistant closure or continuous thread closure with pulp and heat seal liner with or without silica gel.

Pack sizes include 28’s, 30’s and 90’s tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Ground Floor, Block 1,

Bassonia Estate Office Park (East),

1 Cussonia Drive,

Bassonia Rock Ext 12

Alberton

Gauteng

8. REGISTRATION NUMBERS

SYROMAK 10 ODT: 56/20.2.8/0719

9. DATE OF FIRST AUTHORISATION

SYROMAK 10 ODT: 14 June 2022

10. DATE OF REVISION OF THE TEXT

1 April 2023

The Product has been manufactured under a license from the Medicines Patent Pool

The Products are not for administration to anyone other than Child Patients

Any other use is not authorized

PM0055-01

Vanita Rajool

Digitally signed by Vanita Rajool
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Date: 2023.08.15 11:25:17 +02'00'