Professional Information For:

DALIDUO

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DALIDUO 50/ 25 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DALIDUO (film-coated tablet): Each tablet contains rilpivirine hydrochloride equivalent to 25 mg rilpivirine and dolutegravir sodium equivalent to 50 mg dolutegravir

Each tablet contains sugar and sweeteners 145 mg mannitol and 52 mg lactose monohydrate

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink coloured, capsule shaped biconvex film-coated tablet debossed with “Cipla” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

DALIDUO is indicated for the treatment of immunodeficiency virus-1(HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/ml), for at least 6 months on a stable PI, NI or NNRTI plus NRTI based regimens, without known or suspected resistance to either

antiretroviral component. Co - administration with any other NNRTI medicines is not recommended (**see section 4.5**)

4.2. Posology and method of administration

Posology:

DALIDUO should be initiated by a medical practitioner experienced in the management of HIV infection.

Adults

The recommended dose is one DALIDUO tablet once a day.

Special Populations

Elderly patients:

There is limited data available for the use of dolutegravir, an active component in DALIDUO in patients aged 65 years and over. There is therefore no dose adjustments required for DALIDUO in elderly patients.

Children and adolescents (< 18 years old):

The safety and efficacy of rilpivirine, an active component in DALIDUO has not been proven in adolescents and children. Treatment with rilpivirine, an active component in DALIDUO is not recommended for use in children and adolescents ≤ 18 years.

Renal impairment:

No dose adjustment of DALIDUO is required in patients with renal impairment.

Hepatic impairment

No dosage adjustment of DALIDUO is required in patients with mild hepatic impairment (Child-Pugh score A). DALIDUO is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B and C), see **sections 4.3 and 5.2**.

Patients using rifampicin

Rifampicin decreases the blood levels of dolutegravir.

Method of administration

DALIDUO should be taken orally with food.

4.3 Contraindications

- Hypersensitivity to rilpivirine, dolutegravir or any of the excipients in DALIDUO.
- It is not recommended that DALIDUO be co-administered with other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's) e.g. delavirdine, efavirenz, etravirine, nevirapine, see **section 4.5**.
- DALIDUO should not be used in combination with carbamazepine, oxcarbazepine, phenobarbitone, phenytoin and systemic dexamethasone (except as a single dose treatment), see **section 4.5**.
- Rifabutin, rifampicin and rifapentine are potent inducers of CYP3A enzymes. DALIDUO should not be used in combination with these medicines, see **section 4.5**.
- DALIDUO should not be used concomitantly with products containing St. Johns Wort, see **section 4.5**.
- The proton-pump inhibitors (PPIs) lansoprazole, omeprazole, rabeprazole, pantoprazole and esomeprazole should not be administered concomitantly with DALIDUO, see **section 4.5**.
- DALIDUO is contraindicated in combination with dofetilide and pilsicainide.
- DALIDUO is contraindicated in moderate and severe hepatic impairment.
- Fampridine (also known as dalfampridine).
- Peri-conception, during the first trimester of pregnancy and in lactation.

4.4 Special warnings and precautions for use

- Safety and efficacy of the individual active ingredients in various ART combination regimens with similar dosages as contained in DALIDUO have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the actives combined in a fixed drug combination (FDC) as in DALIDUO have not been established.
- Hypersensitivity reactions have been reported with integrase inhibitors and were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Discontinue DALIDUO 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 DALIDUO or other suspect medicines after the onset of hypersensitivity may result in a life – threatening reaction.
- Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood, other bodily secretion or sexual contact. Appropriate precautions to prevent transmission of HIV should continue to be employed.
- Virologic Failure and Development of Resistance

  In a study, patients treated with rilpivirine with a baseline viral load > 100, 000 HIV-1 RNA copies/ mL had a greater risk of virologic failure compared to patients with a baseline viral load ≤ 100, 000 HIV-1 RNA copies/ mL. Patients with a baseline viral load > 100, 000 HIV-1 RNA copies/ ml who experienced virologic

failure exhibited a higher rate of treatment-emergent resistance to the NNRTI class. Patients who failed virologically on rilpivirine-containing products developed lamivudine/ emtricitabine-associated resistance. This information should be taken into consideration when initiating therapy with DALIDUO.

- Interaction with other medicines

  Caution should be given to prescribing DALIDUO with other medicines that may reduce the exposure of rilpivirine, see **section 4.5**.

  There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicines that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg daily and 300 mg daily) have been shown to prolong the QTc interval of the electrocardiogram, see **section 5.1 and 4.5**. DALIDUO should be used with caution when co-administered with medicines with a known risk of Torsade de Pointes.

- Fat distribution

  Redistribution/ accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo lump), peripheral wasting, facial wasting, breast enlargement, cushingoid appearance and elevated serum lipid and glucose levels have been observed in HIV patients and those receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. 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

Immune reconstitution syndrome has been reported in HIV–infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium complex, cytomegalovirus, Pneumocystis jiroveci (P. carinii)* pneumonia and tuberculosis). This inflammatory response and the underlying infections may necessitate further evaluation and treatment which should not be delayed. Auto-immune disorders (such as Graves disease, polymyositis and Guillain -Barre syndrome) have also 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-infection. 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, higher body mass index), cases of osteonecrosis have 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. DALIDUO is contraindicated in patients with moderate or severe hepatic impairment, see **section 4.3**.

- Opportunistic infections

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

- Patients with hepatitis B or C

  There is no clinical data available in patients with hepatitis B co-infection. Medical practitioners should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus. Limited data is available in patients with hepatitis C co-infection. A higher incidence of liver chemistry elevations (Grade 1) may occur in patients treated with dolutegravir and rilpivirine co-infected with hepatitis C compared to those who were not co-infected. Monitoring of liver function is recommended in patients with hepatitis B and/ or C co-infection. In patients with advanced liver or cirrhosis, treatment discontinuation is not recommended since post - treatment exacerbation of hepatitis may lead to hepatic decompensation.

- DALIDUO contains sugars/ sweeteners such as mannitol which may have a mild laxative effect and lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose - galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

- DALIDUO contains dolutegravir and rilpivirine and any interactions that have been identified with either component individually, may occur with DALIDUO. There are no significant interactions between dolutegravir and rilpivirine. Recommendations are based on either interaction studies or predicted interactions due to expected magnitude of interaction and/or potential for serious effects or loss of potency. DALIDUO is not expected to be co-administered with other HIV-1 antiretroviral medicines and information is provided for reference.

Dolutegravir interactions:

- *In vitro,* dolutegravir had 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, 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, dolutegravir 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), aciclovir, valaciclovir, sitagliptin, adefovir).
- In medicine interaction studies, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethyl estradiol. *In vitro,* dolutegravir inhibited the renal organic cation transporter 2 (OCT2). Based on

this observation, dolutegravir a component of DALIDUO may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, pilsicainide or metformin). See table 1 below: Medicine Interactions – Other Medicines).

- Effect of other medicines on the pharmacokinetics of dolutegravir:

  Dolutegravir is eliminated mainly through metabolism by UGT 1A1. Dolutegravir 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 DALIDUO. Co-administration of dolutegravir and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and / or Pgp may increase dolutegravir plasma concentration (See table 1 below).

  Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require dolutegravir dose adjustment to 50 mg twice daily. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of dolutegravir. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see table below: Medicines 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, bocepravir, telaprevir, prednisone, rifabutin and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dolutegravir dose adjustment is required when co-administered with these medicines.

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

Table 1: Medicine Interactions

Concomitant Medicinal Class: Medicine Name:	**Effect on concentration of dolutegravir or concomitant medicine**	**Clinical comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC↓ 71 % C_{max} ↓ 52 % C_T ↓ 88 % ETR ↔	Etravirine decreased dolutegravir plasma concentrations, which may result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ ritonavir, darunavir/ ritonavir or lopinavir/ ritonavir.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC↓ 57 % C_{max} ↓ 39 % C_T ↓ 75 %	Efavirenz decreased dolutegravir plasma concentrations. Alternative

	EFV ↔	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 concentrations 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. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 49 %	Atazanavir increased dolutegravir plasma concentrations. No

	C_T ↑ 180 % ATV ↔	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 concentrations. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % C_T ↓ 76 % TPV ↔ RTV ↔	Tipranavir/ ritonavir decreases dolutegravir concentrations. Co-administration of DALIDUO with tipranavir/ritonavir is not recommended.
Protease Inhibitor: Fosamprenavir/ ritonavir (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 needed.

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 ↔ C_{max} ↔ C_T ↔ LPV ↔ RTV ↔	Lopinavir/ ritonavir did not change dolutegravir plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ ritonavir (DRV+RTV)	Dolutegravir ↓ AUC ↓ 32 % 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:	Dolutegravir ↔ TDV ↔	Tenofovir did not change dolutegravir

Tenofovir (TDV)		plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ ritonavir + Etravirine (LPV/ RTV + ETR)	Dolutegravir ↔ AUC ↑ 10 % C_{max} ↑ 7 % C_T ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ ritonavir and etravirine did not change dolutegravir plasma concentrations 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 concentrations to a clinically relevant extent. No dose adjustment is necessary.
Other medicines		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration with dolutegravir has the potential to increase

		dofetilide or pilsicainide plasma concentrations via inhibition of OCT2 transporter. Dofetilide or Pilsicainide co-administration with dolutegravir is contraindicated due to the potentially life-threatening toxicity caused by high dofetilide or pilsicanide concentrations, see **section 4.3**
Oxcarbazepine Phenytoin Phenobarbitone Carbamazepine St. Johns wort	Dolutegravir ↓	Co-administration may decrease dolutegravir plasma concentrations. Co-administration with these metabolic inducers is contraindicated.
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 concentrations. Dolutegravir is recommended to be administered 4 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	Dolutegravir is recommended to be administered 4 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 %	Dolutegravir is recommended to be administered 4 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.

Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of DALIDUO with metformin, to maintain glycaemic control.
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_T ↓ 72 %	Rifampicin decreases dolutegravir concentrations. Co administration is contraindicated.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMIN))	Effect of dolutegravir: EE↔ AUC ↑ 3 % C_{max} ↓ 1 % C_T ↑ 2 % Effect of dolutegravir NGMIN ↔ AUC ↓ 2 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is

	C_{max} ↓ 11 % C_T ↓ 7 %	necessary when co-administered with dolutegravir.
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 dolutegravir. Clinical monitoring is recommended as methadone maintenance may need to be adjusted in some patients.
Anticoagulants: Warfarin	Effect of dolutegravir: Anticoagulants ↔	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.

Rilpivirine

Medicines that affect rilpivirine exposure

Rilpivirine is primarily metabolised by cytochrome P450 (CYP3A), and medicines that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of rilpivirine and medicines that induce CYP3A may result in decreased plasma concentrations of rilpivirine (exposure) which could potentially reduce the therapeutic effect of rilpivirine. Co-administration of rilpivirine and medicines that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Co-administration of rilpivirine with medicines that increase gastric pH such as PPIs, may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of DALIDUO.

Medicines that are affected by the use of rilpivirine

QT prolonging medicinal products

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products that prolong the QTc interval of the ECG. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG (see section 5.1). DALIDUO should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

Rilpivirine at a dose of 25 mg (once daily) is not likely to have a clinically relevant effect on the exposure of medicines metabolised by CYP enzymes. Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicines are listed in Table 1 and Table 2, respectively.

Interaction table

Interactions between rilpivirine and co-administered medicines are listed in Table 2 and Table 3 below (increase is indicated as ↑, decrease as ↓, no change as ↔, not applicable as NA.

Table 2: Medicine Interactions- Rilpivirine co-administered with antiretroviral and antiviral medicines					
Co-administered medicine	Dose of co-administered medicine	Medicine assessed	C_{max}	AUC	C_{min}
NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs/N(t)RTIs)					
Didanosine*#	400 mg daily	didanosine	↔	↑ 12 %	NA
		rilpivirine	↔	↔	↔
	No dose-adjustment is required when DALIDUO is co-administered with didanosine. As didanosine is administered on an empty stomach, didanosine should be administered at least 2 hours before or 4 hours after rilpivirine (which should be administered with a meal).				
Tenofovir disoproxil fumarate*#	300 mg daily	Tenofovir	↑ 19 %	↑ 23 %	↑ 24 %
		rilpivirine	↔	↔	↔
	No dose-adjustment is required when rilpivirine is co-administered with tenofovir disoproxil fumarate.				
Other NRTIs abacavir, emtricitabine, lamivudine, stavudine and zidovudine)	Based on the different elimination routes for rilpivirine and these other NRTIs, no clinically relevant interactions are expected between these medicines and rilpivirine				

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)					
NNRTIs delavirdine, efavirenz, etravirine, nevirapine)	It is not recommended to co administer rilpivirine with NNRTIs.				
PROTEASE INHIBITORS (PIs) with co-administration of low-dose ritonavir					
Darunavir/ritonavir*#	800/ 100 mg daily	darunavir	↔	↔	↓ 11 %
		rilpivirine	↑ 79 %	↑ 130 %	↑ 178 %
	Concomitant use of rilpivirine with darunavir/ ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when rilpivirine is co administered with darunavir/ ritonavir.				
Lopinavir/ritonavir (soft gel capsules) *#	400/100 mg twice daily	Lopinavir	↔	↔	↓ 11 %
		rilpivirine	↑ 29 %	↑ 52 %	↑ 74 %
	Concomitant use of rilpivirine with lopinavir/ ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when rilpivirine is co administered with lopinavir/ ritonavir				
Other boosted PIs (atazanavir/ ritonavir, fosamprenavir/ rito-navir, saquinavir/ ritonavir, tipranavir/ ritonavir|)	Concomitant use of rilpivirine with boosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.				

PROTEASE INHIBITORS (PIs) – without co-administration of low dose ritonavir

Unboosted PIs (atazanavir, Fosamprenavir, indinavir, nelfinavir)	Concomitant use of rilpivirine with unboosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.
CCR5 ANTAGONISTS	
Maraviroc	No clinically relevant interaction is expected when rilpivirine is co-administered with maraviroc.
INTEGRASE STRAND TRANSFER INHIBITORS	
Raltegravir	No clinically relevant interaction is expected when rilpivirine is co-administered with raltegravir. No dose adjustment is necessary.
OTHER ANTIVIRAL MEDICINES	
Ribavirin	No clinically relevant interaction is expected when DALIDUO is co-administered with ribavirin.
	*The Interaction between rilpivirine was evaluated in a clinical study. All other medicine interactions shown may have been predicted. · #This interaction study was performed with a dose higher than the recommended dose for rilpivirine assessing the maximal effect on the co-administered medicine. The dosing recommendation is applicable to the recommended dose of 25 mg rilpivirine daily.

Table 3: Medicine interactions- Rilpivirine co-administered with non-antiretroviral medicines

Co-administered medicine	Dose of co-administered	Medicine assessed	C_{max}	AUC	C_{min}

	medicine				
ANTICONVULSANTS					
Carbamazepine, Oxcarbazepine, Phenobarbitone Phenytoin	rilpivirine should not be used in combination with these anticonvulsants as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of DALIDUO, see **section 4.3**.				

AZOLE ANTIFUNGAL MEDICINES					
Ketoconazole *#	400 mg daily	Ketoconazole rilpivirine	↔ ↑ 30 %	↓ 24 % ↑ 49 %	↓ 66 % ↑ 76 %
Fluconazole, Itraconazole, Posaconazole, Voriconazole	Concomitant use of rilpivirine with azole antifungal medicines may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when rilpivirine is co-administered with azole antifungal medicines.				

ANTIMYCOBACTERIALS					
Rifabutin *#	300 mg daily	Rifabutin 25-*O*-desacetyl-rifabutin rilpivirine	↔ ↔ ↓ 35 %	↔ ↔ ↓ 46 %	↔ ↔ ↓ 49 %
	Rilpivirine should not be used in combination with rifabutin as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of DALIDUO.				

Rifampicin*#	600 mg daily	rifampicin 25-desacetyl-rifampicin rilpivirine	↔ ↔ ↓ 69 %	↔ ↓ 9 % ↓ 80 %	NA NA ↓ 89 %
Rifapentine	Rilpivirine should not be used in combination with rifampicin as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of DALIDUO, **see section 4.3**.				

MACROLIDE ANTIBIOTICS	
Clarithromycin, Erythromycin, Troleandomycin	Concomitant use of rilpivirine with clarithromycin, erythromycin and troleandomycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.
GLUCOCORTICOIDS	
Dexamethasone (systemic)	Rilpivirine should not be used in combination with systemic dexamethasone as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of rilpivirine. Alternatives should be considered, particularly for long-term use, see **section 4.3**.

PROTON PUMP INHIBITORS					
Omeprazole *#	20 mg daily	Omeprazole	↓ 14 %	↓ 14 %	NA

		rilpivirine	↓ 40 %	↓ 40 %	↓ 33 %
Lansoprazole, Rabeprazole Pantoprazole Esomeprazole	Rilpivirine should not be used in combination with proton pump inhibitors as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). This may result in loss of therapeutic effect of DALIDUO, see **section 4.3**.				

H_2-RECEPTOR ANTAGONISTS					
Famotidine *#	40 mg single dose taken 12 hours before rilpivirine	rilpivirine	↔	↓ 9 %	NA
	40 mg single dose taken 2 hours before rilpivirine	rilpivirine	↓ 85 %	↓ 76 %	NA
	40 mg single dose taken 4 hours after rilpivirine	rilpivirine	↑ 21 %	↑ 13 %	NA

Cimetidine, Nizatidine Ranitidine	The combination of rilpivirine and H_2-receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H_2-receptor antagonists should only be administered atleast12 hours before or at least four hours after DALIDUO.
ANTACIDS	
Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	The combination of rilpivirine and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). Antacids should only be administered either at least two hours before or at least four hours after DALIDUO.

NARCOTIC ANALGESICS					
Methadone *	60-100 mg daily, Individualised dose	R (-) methadone S (+) methadone	↓ 14 % ↓ 13 %	↓ 16 % ↓ 16 %	↓ 22 % ↓ 21 %
	No dose-adjustments are required when initiating co-administration of methadone with rilpivirine. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.				
HERBAL PRODUCTS					
St John's Wort (Hypericum perforatum)	Rilpivirine should not be used in combination with products containing St John's wort as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of DALIDUO, see **section 4.3**.				

ANALGESICS					
Acetaminophen *# (paracetamol)	500 mg single dose	acetaminophen rilpivirine	↔ ↔	↔ ↔	NA ↑ 26 %
	No dose-adjustments are required when rilpivirine is co-administered with acetaminophen (paracetamol).				
OESTROGEN-BASED CONTRACEPTIVES					
Ethinyloestradiol* Norethindrone•	0,035 mg daily 1 mg daily	Ethinyloestradiol Norethindrone	↑ 17 % ↔	↔ ↔	↔ ↔

	No dose-adjustment is required for the concomitant use of rilpivirine and oestrogen and/or progesterone-based contraceptives.

HMG CO-A REDUCTASE INHIBITORS					
Atorvastatin *#	40 mg daily	atorvastatin rilpivirine	↑ 35 % ↓ 9 %	↔ ↔	↓ 15 % ↔
Ruvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	No dose-adjustment is required when rilpivirine Is co-administered with an HMG co-A reductase inhibitor				

PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITOR					
Sildenafil *#	50 mg single dose	sildenafil rilpivirine	↔ ↔	↔ ↔	NA ↔
Vardenafil Tadalafil	No dose-adjustment is required when rilpivirine Is co-administered with a PDE-5 inhibitor				

ANTIARRHYTHMICS		
Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration

Digoxin/ Dolutegravir Digoxin/ Rilpivirine[1]	Dolutegravir ↔ (Not studied) Rilpivirine ↔ Digoxin AUC ↔ C_{min} NA C_{max} ↔	No dose adjustment is required.

Concomitant Medicine class: Medicine Name	Effect on concentration of Rilpivirine or concomitant Medicine	Clinical comment
Anticoagulants: Warfarin	Effect of rilpivirine: Anticoagulants ↔	No dose adjustment is necessary

*The interaction between rilpivirine and the medicine was evaluated in a clinical study. All other interactions shown are predicted.

This interaction study has been performed with a dose higher that the recommended dose for rilpivirine assessing the maximal effect on the co-administered medicine. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg daily.

[1] The interaction between dolutegravir and/or rilpivirine and the medicinal product was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

4.6. Fertility, pregnancy and lactation

Women of child-bearing potential

Adequate contraception Is recommended for women of childbearing potential when taking DALIDUO.

Pregnancy:

Safe use during pregnancy has not been established. The effect of dolutegravir on human pregnancy is unknown. In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. DALIDUO is contraindicated in peri, preconception period and the first trimester of pregnancy (**see section 4.3**).

Treatment with DALIDUO should not be started without a medically/laboratory supervised negative pregnancy (urine and/or blood test, repeated at frequent intervals as needed. There is some evidence of neural tube defects with the use of dolutegravir, as contained in DALIDUO, if started at the time of conception or early pregnancy.

DALIDUO should not be prescribed to women who plan to become pregnant. Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and post-partum. The pharmacokinetic data demonstrated that total exposure (AUC) rilpivirine as a part of an antiretroviral regimen was approximately 30 % lower during pregnancy compared with post-partum (6-12 weeks) Studies in rats and rabbits with rilpivirine have shown no evidence of relevant embryonic or foetal toxicity, effect on reproductive function, or teratogenicity.

4.7. Lactation:

Safe use during lactation has not been established.

HIV infected women should not breastfeed their infants in order to avoid transmission of HIV. It is expected that dolutegravir will be secreted into human milk. It is not known whether rilpivirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving DALIDUO.

Fertility

Animal studies indicate no effect of dolutegravir or rilpivirine on male or female fertility.

4.8. Effects on ability to drive and use machines

DALIDUO may influence the ability to drive and use machines.

Dizziness and somnolence may occur. Patients should ensure that they do not engage in driving or operating machines until they know how DALIDUO affects them.

4.9. Undesirable effects

a) Summary of the safety profile

Dolutegravir

Adverse drug reactions (ADRs) identified in an analysis of pooled data from clinical studies are listed below by system organ class and by frequency. Frequencies are defined as: frequent, less frequent or unknown. The safety profile was similar across the treatment naïve, treatment experienced (and integrase naïve) and integrase resistant patient populations.

b) Tabulated (or structured listing) summary of adverse reactions

List of adverse reactions

The following adverse reactions are reported corresponding to: Frequent, Less Frequent and Frequency Unknown:

Adverse reactions associated with the fixed dosed combination of dolutegravir and rilpivirine in DALIDUO

Blood and lymphatic systems disorders

Frequent: decreased white blood cell count, decreased haemoglobin, decreased platelet count

Immune system disorders

Less Frequent: hypersensitivity

Frequency unknown: immune reconstitution syndrome

Metabolism and nutrition disorders

Frequent: increased total cholesterol (fasted), increased LDL cholesterol (fasted), decreased appetite, increased triglycerides (fasted)

Psychiatric disorders

Frequent: insomnia, abnormal dreams, depression, sleep disorders, depressed mood, anxiety

Less Frequent: suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)

Nervous system disorders

Frequent: headache, dizziness, somnolence

Gastrointestinal disorders

Frequent: nausea, increased pancreatic amylase, diarrhoea, abdominal pain, vomiting, flatulence, increased lipase, abdominal discomfort, upper abdominal pain, dry mouth

Hepatobiliary disorders

Frequent: increased transaminases (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations), increased bilirubin

Less frequent: hepatitis, acute hepatic failure**

Skin and subcutaneous tissue disorders

Frequent: rash, pruritus

Musculoskeletal and connective tissue disorders

Less Frequent: arthralgia, myalgia

General disorders and administration site conditions

Frequent: fatigue

Investigations

Frequent: creatine phosphokinase (CPK) elevations

** This adverse reaction was identified through post-marketing surveillance for dolutegravir in combination with

other ARVs. The frequency category of rare was estimated based on post-marketing reports.

Adverse reactions associated with dolutegravir, the individual active component of DALIDUO (dolutegravir and rilpivirine):

Immune System Disorders

Less Frequent: hypersensitivity, Immune Reconstitution Syndrome

Psychiatric Disorders

Frequent: Insomnia

Nervous System Disorders

Frequent: headache, dizziness, abnormal dreams

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

Adverse reactions associated with rilpivirine, the individual active component of DALIDUO (dolutegravir and rilpivirine):

Blood and lymphatic system disorders

Frequent: increased AST, increased pancreatic amylase

Less Frequent: decreased haemoglobin, decreased platelet count, decreased white

blood cell count

Frequency Unknown: increased creatinine

Metabolism and nutrition disorders

Less Frequent: decreased appetite, increased total cholesterol (fasted), increased LDL cholesterol (fasted), increased triglycerides (fasted)

Psychiatric Disorders

Frequent: depression, insomnia,

Less Frequent: abnormal dreams, sleep disorders, depressed mood

Nervous System Disorders

Frequent: headache

Less Frequent: dizziness, somnolence

Gastrointestinal Disorders

Less Frequent: abdominal pain, nausea, vomiting, abdominal discomfort, increased lipase

Hepatobiliary disorders

Less frequent: increased ALT, increased bilirubin

Skin and Subcutaneous Tissue Disorders

Frequent: rash

General disorders and administration site conditions

Less Frequent: fatigue

Investigations

Frequent: transaminases increased

c) Description of selected adverse reactions

Dolutegravir

Changes in laboratory chemistries

Increases in serum creatinine may have occurred within the first week of treatment with dolutegravir 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 5.2** – effects on renal function.

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir and raltegravir (but not efavirenz) arms in the programme. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1). See **section 5.2** – metabolism. Asymptomatic creatinine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy. **(2: E1)**

Rilpivirine

There may be changes from baseline in total cholesterol, LDL- cholesterol, HDL - cholesterol and triglycerides. The impact of such findings has not been demonstrated.

Lipodystrophy

Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV-infected patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump), see **section 4.4**.

Immune reconstitution 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 (immune reconstitution syndrome), see **section 4.4**.

d) Other special populations

Rilpivirine

Patients co-infected with hepatitis B and/or hepatitis C virus

In patients co-infected with hepatitis B or C virus receiving rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving rilpivirine who were not co-infected. The pharmacokinetic exposure of rilpivirine in co-infected patients was comparable to that in patients without co-infection.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the 6.04 Adverse Drug Reaction Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd. (by e-mail: drugsafetysa@cipla.com).

4.10. 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 DALIDUO. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary such as monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. DALIDUO is highly bound to plasma proteins, it is unlikely that it will be significantly be removed by dialysis. If indicated, elimination of unabsorbed rilpivirine may be removed by administration of activated charcoal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 20.2.8 Antiviral medicines

Mechanism of Action:

Dolutegravir

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 HV replication cycle. *In vitro,* dolutegravir dissociates slowly from the active site of the wild type integrase–DNA complex ($t_{1/2}$ 71 hours)

Rilpivirine

Rilpivirine Is a diarylpyrimidine NNRTI of HIV. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β and γ.

Antiviral activity in vitro

Rilpivirine exhibited activity against laboratory strains of wild type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-M1/IIIB of 0,73 nM (0,27 ng/mL). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2 510 to 5 220 nM (920 to 1 910 ng/mL), treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B,C, D, F, G, H) primary isolates with EC_{50} values ranging from 0,07 to 1,01 nM (0,03 to 0,37 ng/mL) and group O primary isolates with EC_{50} values ranging from 2,88 to 8,45 nM (1,06 to 3,10 ng/mL).

Rilpivirine showed additive antiviral activity in combination with the N (t)RTIs abacavir, didanosine, emtricitabine, stavudine and tenofovir; the PIs amprenavir, atazanavir,

darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide. Rilpivirine also shows additive to synergistic antiviral activity in combination with the NRTIs lamivudine and zidovudine, and the integrase inhibitor raltegravir.

Mechanism of resistance:

Dolutegravir

Resistance in vitro

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir were not observed during HIV -1 passage. during wild-HIV1 passage in the presence of dolutegravir integrase substitutions observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,2 for strain NL 432. Additional passage of wildtype subtype B, C and A/G viruses in the presence of dolutegravir selected for R263K, G118R and S153T.

Anti-HIV Activity Against Resistant Strains: Reverse Transcriptase Inhibitor and Protease Inhibitor Resistant Strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 PI-resistant-HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wildtype strain.

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. **(2: A8)**

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. Treatment of HIV-2 infections with rilpivirine is not recommended in the absence of clinical data.

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 once daily in treatment-naïve studies (SPRING-1, SPRING -2 and SINGLE studies). In a SAILING study for treatment experienced (and integrase naïve) patients (n=354 in 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.

Rilpivirine

In cell culture

Rilpivirine resistant strains were selected in cell culture starting from wild type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The most commonly observed amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

A biological cut off (BCO) for rilpivirine was determined at the fold change In EC_{50} value (FC) of 3, 7 on the basis of the analysis of the susceptibility of a large panel of HIV-1 wild type

recombinant clinical isolates.

Cross resistance

Site-directed NNRTI mutant virus

In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96 %) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I andY181V.

Recombinant clinical isolates

Rilpivirine retained sensitivity (FC s BCO) against 62% of 4 786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Effects on QTc Interval

The effect of rilpivirine at the recommended dose of 25 mg daily on the QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. rilpivirine, at the recommended dose of 25 mg daily, is not associated with a clinically relevant effect on QTc interval.

When supratherapeutic doses of 75 mg daily and 300 mg daily of rilpivirine were studied in healthy adults there was a dose related QTcF prolongation. The maximum mean time-matched (95 %upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10,7 (15,3) and 23,3 (28,4) ms, respectively. Steady-state administration of rilpivirine 75 mg daily and 300 mg daily resulted in a mean Cmax approximately 2,6-fold and 6,7 -fold, respectively, higher than the mean steady-state Cmax observed with the recommended 25 mg daily dose of rilpivirine.

Pharmacokinetic/ Pharmacodynamic (PK/PD) relationship:

5.2. Pharmacokinetic properties

Dolutegravir

Dolutegravir pharmacokinetics 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 CV_b % for AUC and C_{max} ranged from ~ 20 to 40 % and C_T 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.

Rilpivirine

The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in adult antiretroviral treatment-naive HIV-1 infected patients. Exposure to rilpivirine was generally lower in HIV-1 infected patients than in healthy subjects

Absorption

Dolutegravir

Dolutegravir is absorbed following oral administration, with median T_{Max} at 2 or 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 non-linear 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 33 %, 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 have not been established.

Rilpivirine

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within four to five hours. The absolute bioavailability of rilpivirine is unknown.

Effect of food on absorption

The exposure to rilpivirine was approximately 40 % lower when rilpivirine was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high fat high caloric meal (928 kcal). When rilpivirine was taken with only a protein rich nutritional drink, exposures were 50 % lower than when taken with a meal.

Distribution

Dolutegravir

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 ICSO); CSF: plasma concentration ratio of dolutegravir ranged from 0,11 to 1 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, see **section 5.2**.

Rilpivirine

Rilpivirine is approximately 99,7 % bound to plasma proteins in vitro primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g. cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

Dolutegravir

Dolutegravir is primarily metabolised via UGT1A 1 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).

Rilpivirine

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP3A) system.

Elimination

Dolutegravir

Dolutegravir has a terminal half-life of -14 hours and an apparent clearance (CUF) of 0,56 L/ hr. 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).

Rilpivirine

The terminal elimination hail-life of rilpivirine is approximately 45 hours. After single-dose oral administration of ^{14}C rilpivirine, on average 85 % and 6,1 % of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25 % of the administered dose. Only trace amounts of unchanged rilpivirine (< 1 % of dose) were detected in urine.

Special Populations

Paediatric

Rilpivirine

Dosing recommendations for paediatric patients cannot be made due to insufficient data. DALIDUO is not recommended for use in patients under 18 years of age, see **section 4.2**.

Elderly

Dolutegravir

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 of > 65 years old are limited.

Rilpivirine

Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine Pharmacokinetics is not different across the age range (18 to 78 years) evaluated. No dose adjustment is required in elderly patients.

Renal Impairment

Dolutegravir

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 heathy 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.

Rilpivirine

The pharmacokinetics of rilpivirine has not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. Therefore, the impact of renal impairment on rilpivirine elimination is expected to be minimal. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic Impairment

Dolutegravir

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.

Rilpivirine

Rilpivirine is primarily metabolised and eliminated by the liver. In a study comparing eight patients with mild hepatic impairment (Child-Pugh score A) to eight matched controls, and eight patients with moderate hepatic impairment (Child-Pugh score B) to eight matched controls, the multiple dose exposure of rilpivirine was 47 % higher in patients with mild hepatic impairment and 5 % higher in patients with moderate hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic

impairment (Child-Pugh A or B). Rilpivirine has not been studied in patients with severe hepatic ~~I~~impairment (Child-Pugh score C).

Polymorphisms in metabolising enzymes

Dolutegravir

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 NR112 were not associated with differences in the pharmacokinetics of dolutegravir. Rilpivirine pharmacokinetics are not anticipated to be impacted by polymorphisms in drug metabolising enzymes.

Co-infection with Hepatitis B or C

Dolutegravir

Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir.

Rilpivirine

Population pharmacokinetic analysis indicated that hepatitis B and/or C virus co-infection had no clinically relevant effect on the exposure to rilpivirine. Subjects with hepatitis B co-infections were excluded from studies with dolutegravir/rilpivirine tablet.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core

Mannitol

Microcrystalline Cellulose

Sodium Starch Glycolate

Povidone

Colloidal Silicon Dioxide

Sodium Stearyl Fumarate

Lactose Monohydrate

Polysorbate 20

Croscarmellose Sodium

Ferric Oxide Yellow

Silicified Microcrystalline Cellulose

Magnesium Stearate

Film coating

Opadry II pink

List of components of Opadry II pink:

Polyvinyl Alcohol-Part Hydrolyzed

Macrogol/PEG (MW 3350, MACROGOL 4000 JP)

Talc

Titanium Dioxide

Iron Oxide Yellow

Iron Oxide Red

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep the bottle tightly closed.

Keep away from children.

6.5. Nature and contents of container

DALIDUO is packed in a 50 cc white round HDPE Bottle consisting of a Silica Gel Bag 2 gm Stripax (Multisorb) R/F and closed with a 33 mm Blue Child Resistant Cap. The HDPE bottle is packed into an outer cardboard carton. Pack sizes are 28 and 30 tablets.

6.6. Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

1474 South Coast Road

Mobeni

Durban

4052

Customer Care: 080 222 6662

E-mail: info@cipla.co.za

8. REGISTRATION NUMBER(S)

55/20.2.8/0301

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 November 2021

Date of latest renewal: TBC

10. DATE OF REVISION OF THE TEXT

20 February 2024