JASUPA
Film-coated tablets

SCHEDULING STATUS:

S4

1. NAME OF MEDICINE:

JASUPA

(Dolutegravir 50 mg/Rilpivirine Hydrochloride 25 mg)

Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains 50 mg of dolutegravir (as dolutegravir sodium) and 25 mg of rilpivirine (as rilpivirine hydrochloride).

Contains sugar (as lactose monohydrate 55,15 mg/tablet and D- mannitol 203,14 mg/tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Film-coated tablets.

Pink, film-coated, oval, biconvex tablets debossed with ‘SV J3T’ on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

JASUPA is indicated for the treatment of human 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 protease inhibitor (PI), integrase strand transfer inhibitor (INSTI) or non-nucleoside reverse transcriptase inhibitor (NRTI) plus nucleoside reverse transcriptase inhibitor (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:

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

If the patient misses a dose of JASUPA, the patient should take it with a meal as soon as they remember, if it is more than 12 hours until the next dose. If the next dose is due within 12 hours, the patient should skip the missed dose and resume the usual dosing schedule.

Separate preparations of dolutegravir and rilpivirine should be used, where dose adjustment or discontinuation of one of the individual components is indicated (see section 4.5).

In these cases, the medical practitioner should refer to the individual professional information.

Adults: The recommended dose of JASUPA in adults is one tablet once daily, taken orally with a meal.

Adolescents and Children: JASUPA is not recommended in paediatric patients below 18 years of age due to insufficient safety and efficacy data.

Elderly: No dose adjustment of JASUPA is required in elderly patients. There are limited data available on the use of JASUPA in patients aged 65 years and over (see section 5.2 Special Patient Populations).

Renal impairment*:* No dosage adjustment of JASUPA is required in patients with renal impairment (see section 5.2 Special Patient Populations).

Hepatic impairment: No dosage adjustment of JASUPA is required in patients with mild hepatic impairment (Child-Pugh score A). JASUPA is contraindicated in severe hepatic impairment (Child-Pugh score B and C) (see section 4.3 and section 5.2 Special Patient Populations).

4.3 Contraindications:

JASUPA is contraindicated in patients with known hypersensitivity to dolutegravir or rilpivirine or to any of the excipients of JASUPA listed in section 6.1.

JASUPA is contraindicated in patients with severe hepatic impairment. JASUPA is contraindicated in combination with the following (see section 4.5):

- products with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to antidysrhythmic medicines dofetilide or pilsicainide, or the potassium channel blocker fampridine (also known as dalfampridine).
- anticonvulsants carbamazepine, oxcarbazepine, phenobarbitone, phenytoin antimycobacterials rifampicin, rifapentine
- proton pump inhibitors (such as omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole)
- glucocorticoid systemic dexamethasone (except as a single dose treatment)
- St John's wort (*Hypericum perforatum)*
- Pre and peri-conception period, during the first trimester of pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use:

Safety and efficacy of the individual active ingredients in various ART combination regimes with similar dosages as contained in JASUPA 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 JASUPA have not been established.

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir as in JASUPA and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. JASUPA and other suspected medicines should be discontinued 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 JASUPA 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 (IRIS):

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 of IRIS include tuberculosis, cytomegalovirus retinitis, generalised and/or focal atypical mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. 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 JASUPA 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, higher 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.

Patients with HIV and hepatitis B or C virus co-infection:

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.
Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines. Patients co-infected with HIV and HBV who discontinue JASUPA should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Interactions with other medicines:

Caution should be given to prescribing JASUPA with medicines that may reduce the exposure of dolutegravir or rilpivirine (see section 4.5).

Opportunistic infections:

Patients receiving JASUPA 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:

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.

JASUPA contains lactose: Patients with rare hereditary problems of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption or intolerance should not use JASUPA (see section 2).

4.5 Interactions with other medicines and other forms of interaction:

JASUPA contains dolutegravir plus rilpivirine and any interactions that have been identified with either component individually, may occur with JASUPA. There are no significant interactions between dolutegravir and rilpivirine.

Effect of Dolutegravir/Rilpivirine on the Pharmacokinetics of Other Medicines:

Effect of Dolutegravir on the Pharmacokinetics of Other Medicines:

Dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of cytochrome P450 enzymes, uridine diphosphate glucuronosyl transferase (UGT), or the transporters P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, multidrug resistance-associated protein (MRP) 2 or MRP4.

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50} > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, UGT1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MRP2 or MRP4. *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, abacavir, zidovudine, maraviroc, opioid analgesics, antidepressants, statins, azole antifungals, proton pump inhibitors, erectile dysfunction agents, aciclovir, valaciclovir, sitagliptin, adefovir).

In medicine interaction studies, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, ritonavir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, boceprevir, daclatasvir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibited the renal OCT2 (IC_{50} = 1,93 μM), multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6,34 μM) and MATE2-K (IC_{50} = 24,8 μM). *In-vivo* dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 without affecting glomerular filtration (see section 4.8 Changes in laboratory chemistries and section 5.1 Effects on Renal Function). Given the *in vivo* exposure, dolutegravir has a low potential to affect the transport of MATE2-K substrates *in vivo*. *In vivo* dolutegravir increases plasma concentrations of medicines in which excretion is dependent upon OCT2 or MATE1 (for example dofetilide, pilsicainide, fampridine (also known as dalfampridine) or metformin) (see Table 1).

In vitro, dolutegravir inhibited the basolateral renal transporters: OAT1 (IC_{50} = 2,12 μM) and OAT3 (IC_{50} = 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 Rilpivirine on the Pharmacokinetics of Other Medicines:

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.

Based on different elimination routes for rilpivirine no clinically relevant interactions are expected with the following medications: abacavir, emtricitabine, lamivudine, maraviroc, ribavirin, stavudine and zidovudine.

Rilpivirine inhibits P-gp *in vitro* (IC_{50} is 9,2 μM). In a clinical study, rilpivirine did not significantly affect the pharmacokinetics of digoxin. However, it may not be completely excluded that rilpivirine can increase the exposure to other medicines transported by P-gp that are more sensitive to intestinal P-gp inhibition, e.g., dabigatran etexilate.

Interactions with medicines are listed in Table 1.

Effect of Other Medicines on the Pharmacokinetics of Dolutegravir/ Rilpivirine:

Effect of Other Medicines on the Pharmacokinetics of Dolutegravir:

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

Co-administration of dolutegravir and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 1).

In vitro, dolutegravir is not a substrate of human OATP1B1, OATP1B3, or OCT1, therefore medicines that solely modulate these transporters are not expected to affect dolutegravir plasma concentration.

Dolutegravir should not be co-administered with polyvalent cation-containing antacids. JASUPA is recommended to be administered at least 4 hours before or 6 hours after taking antacid products.

Interactions with medicines are listed in Table 1.

Effect of Other Medicines on the Pharmacokinetics of Rilpivirine:

Rilpivirine is primarily metabolised by CYP3A and medicines that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see section 5.2). Co-administration of rilpivirine with medicines that induce CYP3A may result in decreased plasma concentrations of rilpivirine 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 may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of rilpivirine.

Interactions with medicines are listed in Table 1.

QT prolonging medicines:

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 once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram (see section 5.1). JASUPA should be used with caution when co-administered with a medicine with a known risk of Torsade de Pointes.

Table 1 - Medicine Interactions:

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicines are listed in Table 1. The below list of interactions is not all-inclusive. Recommendations are based on either interaction studies or predicted interactions due to the expected magnitude of interaction and/or potential for serious adverse events or loss of efficacy. JASUPA is not expected to be co-administered with other HIV-1 antiviral agents and information is provided for reference.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitors: Delavirdine, Efavirenz, Etravirine, Nevirapine	Dolutegravir ↓ Rilpivirine ↓ (↑ with delavirdine)	Co-administration of JASUPA with another NNRTI is not recommended.
Protease Inhibitor (PI): Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 50 % Cτ ↑ 180 % ATV ↔ Rilpivirine ↑	Atazanavir may increase dolutegravir/rilpivirine plasma concentrations. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV/RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 34 % Cτ ↑ 121 % ATV ↔ RTV ↔ Rilpivirine ↑	Atazanavir/ritonavir may increase dolutegravir/rilpivirine plasma concentrations. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV/RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % Cτ ↓ 76 % TPV ↔ RTV ↔ Rilpivirine ↑	Tipranavir/ritonavir may increase rilpivirine plasma concentrations and decreases dolutegravir concentrations. Co-administration of JASUPA with tipranavir/ritonavir is not recommended.

Concomitant Medicine Class: **Medicine Name**	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Protease Inhibitor: Fosamprenavir/ ritonavir (FPV/RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % Cτ ↓ 49 % FPV ↔ RTV ↔ Rilpivirine ↑	Fosamprenavir/ritonavir may increase rilpivirine plasma concentrations and decrease dolutegravir concentrations. No dose adjustment is necessary.
Protease Inhibitors: Fosamprenavir Indinavir Nelfinavir Saquinavir	Dolutegravir ↔ Rilpivirine ↑	Unboosted protease inhibitors may increase rilpivirine plasma concentrations. An increase in dolutegravir plasma concentrations is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV+RTV) †	Dolutegravir ↔ AUC ↓ 4 % C_{max} ↔ Cτ ↓ 6 % LPV ↔ RTV ↔ Rilpivirine ↑ AUC ↑ 52 % C_{max} ↑ 29 % C_{min} ↑ 74 %	Lopinavir/ritonavir did not change dolutegravir/rilpivirine plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Protease Inhibitor: Darunavir/ritonavir (DRV+RTV) †	Dolutegravir ↓ AUC ↓ 22 % C_{max} ↓ 11 % Cτ ↓ 38 % DRV ↔ RTV ↔ Rilpivirine ↑ AUC ↑ 130 % C_{max} ↑ 79 % C_{min} ↑ 178 %	Darunavir/ritonavir did not change dolutegravir/rilpivirine plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir disoproxil fumarate†	Dolutegravir ↔ AUC ↔ C_{max} ↓3 % Cτ ↓ 8 % Effect of dolutegravir: Tenofovir ↔ AUC ↑ 12 % C_{max} ↑ 9% Cτ ↑ 19 % Rilpivirine ↔ Effect of rilpivirine: Tenofovir ↑ AUC ↑ 23 % C_{max} ↑ 19 % C_{min} ↑ 24 %	Tenofovir did not change dolutegravir/rilpivirine plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Nucleoside Reverse Transcriptase Inhibitor: Didanosine†	Dolutegravir ↔ Rilpivirine ↔ Effect of rilpivirine: Didanosine ↔ AUC ↑ 12 % C_{max} ↔ C_{min} NA	Didanosine did not change rilpivirine plasma concentrations to a clinically relevant extent. No dose adjustment of JASUPA is necessary. Didanosine should be administered on an empty stomach at least 2 hours before or 4 hours after JASUPA (which should be taken with a meal).
Integrase Strand Transfer Inhibitor: Raltegravir	Rilpivirine ↔ Effect of rilpivirine: Raltegravir ↑ AUC ↑ 9 % C_{max} ↑ 10 % C_{min} ↑ 27 %	No dose adjustment is necessary.
Other Antiviral Medicines		
Daclatasvir	Dolutegravir ↔ AUC ↑ 33 % C_{max} ↑ 29 % $C\tau$ ↑ 45 % Daclatasvir ↔ Rilpivirine ↔	Daclatasvir did not change dolutegravir plasma concentrations to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentrations. No dose adjustment is necessary.
Simeprevir	Rilpivirine ↔ AUC ↔ C_{max} ↔ C_{min} ↑ 25 % Simeprevir ↔ AUC ↔ C_{max} ↑ 10 % C_{min} ↔ Dolutegravir ↔	No dose adjustment is necessary.
Other Medicines		

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Dofetilide Pilsicainide	Effect of dolutegravir: Dofetilide ↑ Pilsicainide ↑	Co-administration of JASUPA with dofetilide or pilsicainide is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentrations.
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; coadministration has not been studied. Fampridine co-administration with JASUPA is contraindicated (see section 4.3).
Anticonvulsants: Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Effect of carbamazepine: Dolutegravir ↓ AUC ↓ 49 % C_{max} ↓ 33 % Cτ ↓ 73 % Rilpivirine ↓	Metabolic inducers may significantly decrease dolutegravir/rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of JASUPA with these metabolic inducers is contraindicated (see section 4.3).
Herbal products: St. John's wort (*Hypericum perforatum*)	Dolutegravir ↓ Rilpivirine ↓	Co-administration of JASUPA with products containing St. John's wort may significantly decrease dolutegravir/rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of JASUPA with products containing St. John's wort is contraindicated (see section 4.3).

Concomitant Medicine Class: **Medicine Name**	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Proton Pump Inhibitors: Omeprazole† Lansoprazole Rabeprazole Pantoprazole Esomeprazole	Dolutegravir ↔ Rilpivirine (by omeprazole) AUC ↓ 40 % C_{max} ↓ 40 % C_{min} ↓ 33 % Omeprazole (by rilpivirine) AUC ↓14 % C_{max} ↓14 % C_{min} NA	Proton pump inhibitors may significantly decrease rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of JASUPA with proton pump inhibitors is contraindicated (see section 4.3).
H_2-Receptor Antagonists: Famotidine† Cimetidine Nizatidine Ranitidine	Dolutegravir ↔ Rilpivirine: Famotidine taken 12 hours before Rilpivirine AUC ↓ 9 % C_{max} ↔ C_{min} NA Famotidine taken 2 hours before Rilpivirine AUC ↓ 76 % C_{max} ↓ 85 % C_{min} NA Famotidine taken 4 hours after Rilpivirine AUC ↑ 13 % C_{max} ↑ 21 % C_{min} NA	H_2-receptor antagonists may significantly decrease rilpivirine plasma concentrations. JASUPA should be administered at least 4 hours before or at least 12 hours after H_2-receptor antagonists.

Concomitant Medicine Class: **Medicine Name**	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Antacids (e.g., aluminium magnesium hydroxide, and/or calcium carbonate)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 % Rilpivirine ↓	Use with caution as co-administration may significantly decrease dolutegravir/rilpivirine plasma concentrations, resulting in loss of therapeutic effect. JASUPA should be administered at least 4 hours before or 6 hours after taking antacid products.
Calcium or Iron supplements (Non-antacid)	Calcium: Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C24 ↓ 39 % Iron: Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 57 % C24 ↓ 56 %	JASUPA is recommended to be administered at least 4 hours before or 6 hours after taking calcium or iron non-antacid products, or alternatively, co-administer together with a meal.
Metformin	Co-administered with dolutegravir: Metformin ↑ AUC ↑ 79 % C_{max} ↑ 66 % Co-administered with rilpivirine: Metformin ↔ AUC ↔ C_{max} ↔ C_{min} NA	Co-administration of DTG/PRV FDC may increase metformin plasma concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of JASUPA with metformin, to maintain glycaemic control.

Concomitant Medicine Class: **Medicine Name**	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Rifampicin† Rifapentine	Dolutegravir ↓ (by rifampicin) AUC ↓ 54 % C_{max} ↓ 43 % Cτ ↓ 72 % Rifampicin ↔ Rilpivirine ↓ (by rifampicin) AUC ↓ 80 % C_{max} ↓ 69 % C_{min} ↓ 89 %	Rifampicin and rifapentine may significantly decrease dolutegravir/rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of JASUPA with rifampicin or rifapentine is contraindicated (see section 4.3).
Rifabutin	Dolutegravir ↔ Rifabutin ↔ Rilpivirine (25 mg) ↓ AUC ↓ 42 % C_{max} ↓ 31 % C_{min} ↓ 48 % Rilpivirine (50 mg) ↔ (compared to rilpivirine 25 mg alone) AUC ↑ 16 % C_{max} ↑ 43 % C_{min} ↔	Rifabutin decreased the plasma concentrations of rilpivirine. During co-administration with rifabutin an additional 25 mg dose of rilpivirine should be taken at the same time with JASUPA.
Dexamethasone (systemic, except for single dose use)	Rilpivirine ↓ Dolutegravir ↔	Dexamethasone may significantly decrease rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of JASUPA with dexamethasone is contra-indicated, except for single dose use. Alternatives should be considered, particularly for long-term use.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Oral contraceptives (Ethinyl estradiol (EE) and Norelgestromin (NGMN)) Norethindrone	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % Cτ ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % Cτ ↓ 7 % Effect of rilpivirine: EE ↔ AUC ↔ C_{max} ↑ 17 % C_{min} ↔ Effect of rilpivirine: Norethindrone ↔ AUC ↔ C_{max} ↔ C_{min} ↔	Dolutegravir/rilpivirine did not change ethinyl estradiol and norelgestromin/norethindrone plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with JASUPA.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % Cτ ↓ 1 % Effect of rilpivirine: Methadone ↓ AUC ↓ 16 % C_{max} ↓ 14 % Cτ ↓ 22 %	Dolutegravir/rilpivirine did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when initiating co-administration with JASUPA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

Concomitant Medicine Class: **Medicine Name**	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
Azole Antifungals: Ketoconazole† Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ Rilpivirine (by ketoconazole) AUC ↑ 49 % C_{max} ↑ 30 % C_{min} ↑ 76 % Ketoconazole (by rilpivirine) AUC ↓ 24 % C_{max} ↔ C_{min} ↓ 66 %	Azole antifungal agents may increase rilpivirine plasma concentrations. No dose adjustment is necessary.
Clarithromycin Erythromycin	Dolutegravir ↔ Rilpivirine ↑	Clarithromycin and erythromycin may increase rilpivirine plasma concentrations. No dose adjustment is necessary. Where possible, consider alternatives, such as azithromycin.
Digoxin	Dolutegravir ↔ Rilpivirine ↔ AUC ↔ C_{max} ↔ C_{min} NA	No dose adjustment is necessary.
Anticoagulants: Dabigatran etexilate Warfarin	Effect of dolutegravir: Dabigatran ↔ Effect of rilpvirine: Dabigatran ↑ Effect of dolutegravir: Anticoagulants ↔ Effect of rilpvirine: Anticoagulants ↔	The combination of JASUPA and dabigatran etexilate should be used with caution No dose adjustment is necessary

Concomitant Medicine Class: **Medicine Name**	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine***	**Clinical Comment**
HMG CO-A Reductase Inhibitors: Atorvastatin† Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	Dolutegravir ↔ Rilpivirine (by atorvastatin) AUC ↔ C_{max} ↓ 9 % C_{min} ↔ Atorvastatin (by rilpivirine) AUC ↔ C_{max} ↑ 35 % C_{min} ↓ 15 %	No dose adjustment is necessary.
Phosphodiesterase type 5 (PDE-5) inhibitors: Sildenafil† Vardenafil Tadalafil	Dolutegravir ↔ Rilpivirine ↔ AUC ↔ C_{max} ↔ C_{min} ↔ Sildenafil ↔ AUC ↔ C_{max} ↔ C_{min} NA	No dose adjustment is necessary.
Paracetamol (acetaminophen)	Dolutegravir ↔ Rilpivirine ↔ AUC ↔ C_{max} ↔ C_{min} ↑ 26 % Paracetamol (by Rilpivirine) AUC ↔ C_{max} NA C_{min} ↔	No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Medicine*	Clinical Comment

* Where pharmacokinetic parameters are presented, the interaction between dolutegravir and/or 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 than the recommended dose for rilpivirine assessing the maximal effect on the co-administered medicine.

Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration, C_{min} = minimum observed concentration, $C\tau$ = concentration at the end of dosing interval; NA = not assessed

4.6 Fertility, pregnancy and lactation:

Safety in pregnancy and lactation has not been established.

Women of childbearing potential:

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir , as contained in JASUPA,), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of JASUPA in women of childbearing potential to exclude inadvertent (unintentional) use of JASUPA 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:

JASUPA is contraindicated in pre/periconception period and in the first trimester of pregnancy (see section 4.3).

Women of childbearing age should not use JASUPA, unless they are on highly effective contraception.

Treatment with JASUPA 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 JASUPA, if started at the time of conception or in early pregnancy.

Use of dolutegravir, as contained in JASUPA, during pregnancy, 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).

JASUPA should not be prescribed to women who plan to become pregnant. If a pregnancy is confirmed in the first trimester while on dolutegravir, as contained in JASUPA, 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, as contained in JASUPA, 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 (see next paragraph below), but the implications of such exposure are not yet known.

Dolutegravir readily crosses the placenta in humans. In HIV-infected pregnant women, the median (range) foetal umbilical cord concentrations of dolutegravir were 1.28 (1.21 to 1.28) fold greater compared with maternal peripheral plasma concentrations.

There is insufficient information on the effects of dolutegravir on neonates.

Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30 % lower during pregnancy compared with postpartum (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.

Breastfeeding:

HIV infected women should not breastfeed their infants in order to avoid transmission of HIV.

Dolutegravir, as contained in JASUPA, is excreted in human breast milk in small amounts and there is significant exposure to the neonate/infants due to slow elimination; dolutegravir half-life of 33 hours compared to 14 hours in adults.

In an open-label randomised study in which HIV- infected treatment-naïve pregnant women were administered a dolutegravir based regimen until two weeks post-partum, the median (range) dolutegravir breast milk to maternal plasma ratio was 0,033 (0,021 to 0,050).

It is not known if rilpivirine is secreted in human milk.

Mothers taking JASUPA should not breastfeed their infants.

Fertility:

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

4.7 Effects on ability to drive or use machines:

JASUPA may affect the ability to drive and use machines. Patients should ensure that they do not engage in driving or operating machines until they know how JASUPA affects them.

4.8 Undesirable effects:

JASUPA contains dolutegravir plus rilpivirine, therefore the adverse drug reactions (ADRs) associated with these individual components may be expected (Table 2).

Side effects are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 1/1 000) and very rare (< 1/10 000), including isolated reports.

The ADRs observed for dolutegravir plus rilpivirine in analysis of data from clinical trials were consistent with the ADR profiles and severities for the individual components when administered with other antiretroviral agents. No additional ADRs or increased frequency or severity of ADRs were observed with the combination of dolutegravir plus rilpivirine. Treatment-emergent ADRs observed in at least 2 % of subjects in either treatment arm of the pooled analysis of these studies were diarrhoea and headache.

Table 2 Side Effects with the Individual Components of JASUPA

System	Frequency*	Dolutegravir (DTG)	Rilpivirine (RPV)
Immune system disorders	Uncommon	Hypersensitivity (see section 4.4 Special warnings and precautions for use), Immune Reconstitution Syndrome	
Metabolism and nutrition disorders	Common		Decreased appetite
Psychiatric disorders	Common	Insomnia, abnormal dreams, depression, anxiety	Depression, insomnia, abnormal dreams, sleep disorders
	Uncommon	Suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)	Depressed mood
Nervous system disorders	Very common Common Uncommon	Headache Dizziness	 Headache, dizziness Somnolence
Gastrointestinal disorders	Very common	Nausea, diarrhea	
	Common	Abdominal pain Vomiting Flatulence Upper abdominal pain Abdominal discomfort	Abdominal pain Nausea Vomiting
	Uncommon		Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis	

System	Frequency*	Dolutegravir (DTG)	Rilpivirine (RPV)
Skin and subcutaneous tissue disorders	Common	Rash, pruritus	Rash
General disorders and administration site conditions	Common	Fatigue	Fatigue
Investigations	Common		Transaminases increased
* Frequencies are assigned based on the maximum frequencies observed in the pooled SWORD studies or studies with the individual components.			

Changes in laboratory chemistries:

Increases in serum creatinine occurred within the first four weeks of treatment with dolutegravir plus rilpivirine and remained stable through 48 weeks. A mean change from baseline of 8,22 μmol/ℓ (range: -26,5 μmol/ℓ to 51,2 μmol/ℓ) was observed after 48 weeks of treatment. These changes are related to inhibition of active transport and are not considered to be clinically relevant as 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 with dolutegravir plus rilpivirine. 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 creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported.

No clinically relevant differences in lipid profiles were noted throughout the 48 weeks in either treatment group.

Co-infection with Hepatitis B or C:

A higher incidence of liver chemistry elevations (Grade 1) were observed in patients treated with dolutegravir and rilpivirine co-infected with hepatitis C compared to those who were not co-infected. Dolutegravir plus rilpivirine has not been studied in patients with hepatitis B co-infection.

Post-marketing data:

In addition to the side effects included from clinical trial data, below are side effects identified during post-approval use of dolutegravir in combination with other antiretroviral agents. These events have been chosen for inclusion due to a potential causal connection to dolutegravir.

Musculoskeletal and connective disorders: arthralgia, myalgia

Investigations: weight increased.

The following event has been reported in a dolutegravir-containing regimen. The contribution of dolutegravir in this case is unclear.

Hepatobiliary disorders: acute hepatic failure.

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 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:

Experience with overdose of JASUPA, or the individual components, dolutegravir and rilpivirine is limited.

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

There is no specific treatment for overdose with JASUPA. If overdose occurs, the patient should be treated supportively with appropriate monitoring, vital signs and observation of the clinical status of the patient, as necessary. As dolutegravir and rilpivirine are highly bound to plasma proteins, it is unlikely they will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category A 20.2.8 Antiviral agents

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. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2,7 nM and 12,6 nM. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex ($t_{½}$ 71 hours).

Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. 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 cell culture:

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) values of 0,5 nM (0,21 ng per ml) to 2,1 nM (0,85 ng per ml) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.

In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, dolutegravir demonstrated antiviral potency similar to laboratory strains, with a mean EC_{50} of 0,52 nM. When tested in PBMC assays against a panel consisting of 24 HIV-1 clinical isolates (group M (clade A, B, C, D, E, F and G) and group O) and 3 HIV-2 clinical isolates, the geometric mean EC_{50} was 0,20 nM and EC_{50} values ranged from 0,02 to 2,14 nM for HIV-1, while the geometric mean EC_{50} was 0,18 nM and EC_{50} values ranged from 0,09 to 0,61 nM for HIV-2 isolates.

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-1/IIIB of 0,73 nM (0,27 ng per ml). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2 510 to 10 830 nM, 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 (clade A, B, C, D, F, G, H) primary isolates with median EC_{50} values ranging from 0,07 to 1,01 nM and group O primary isolates with EC_{50} values ranging from 2,88 to 8,45 nM.

Antiviral Activity in combination with other antiviral agents:

No medicines with inherent anti-HIV activity were antagonistic with dolutegravir (*in vitro* assessments were conducted in checkerboard format in combination with abacavir, adefovir, amprenavir, efavirenz, enfuvirtide, lopinavir, maraviroc, nevirapine, raltegravir and stavudine). In addition, antivirals without inherent anti-HIV activity (ribavirin) have no apparent effect on dolutegravir activity.

No medicines with inherent anti-HIV activity were antagonistic with rilpivirine (abacavir, amprenavir, atazanavir, darunavir, didanosine, efavirenz, emtricitabine, enfuvirtide, etravirine, indinavir, lamivudine, lopinavir, maraviroc, nelfinavir, nevirapine, raltegravir, ritonavir, saquinavir, stavudine, tenofovir, tipranavir, and zidovudine).

The combination of dolutegravir plus rilpivirine evaluated in an *in vitro* two-medicine combination study showed no antagonistic interactions.

Effect of Human Serum and Serum Proteins:

In vitro studies suggested a 75-fold shift in EC_{50} of dolutegravir in the presence of 100 % human serum (by method of extrapolation), and the protein adjusted EC_{90} (PA-EC_{90}) in PBMCs was estimated to be 64 ng/ml. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve subjects was 1,20 μg/ml, 19 times higher than the estimated PA-EC_{90}.

Resistance in vitro:

Isolation from wild type HIV-1 and activity against resistant strains: Viruses highly resistant to dolutegravir were not observed during the 112 day passage of strain IIIB, with a 4,1-fold maximum fold change (FC) observed for the passaged resistant virus populations with amino acid substitutions at the conserved IN positions S153Y and S153F. Passage of the wild type HIV-1 strain NL432 in the presence of dolutegravir selected for E92Q (passage population virus FC = 3,1) and G193E (passage population virus FC = 3,2) substitutions on Day 56. Additional passage of wild type clade B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

Rilpivirine-resistant strains were selected in cell culture starting from wild type HIV-1 of different origins and clades 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. Resistance to rilpivirine was considered present when FC in EC_{50} value was above the biological cut-off (BCO) of the assay.

Resistance in vivo:

Across the pooled clinical studies, the number of subjects who met the protocol-defined confirmed virologic withdrawal (CVW) criteria was low. Two subjects from each treatment group met CVW criteria at any time through Week 48. NNRTI resistance associated substitution K101K/E mixture with no decreased susceptibility to rilpivirine (FC = 1,2) was observed in one subject with identified adherence issues that received dolutegravir plus rilpivirine. No integrase resistance was observed. This subject's viral load was 1 059 771 copies/ml at the suspected virologic withdrawal visit, and on resumption of dolutegravir plus rilpivirine the viral load decreased to1 018 copies/ml at the confirmatory visit and was < 50 copies/ml at the withdrawal visit. No resistance-associated substitutions were observed for the other three subjects meeting CVW criteria.

Cross resistance:

Site-directed INSTI mutant virus:

Dolutegravir activity was determined against a panel of 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions). The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2,3-fold to 3,6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2,5-fold to 21-fold from reference).

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 (FC ≤ BCO) against 64 (96 %) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N substitution did not result in reduced susceptibility to rilpivirine by itself, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine.

Recombinant clinical isolates:

Dolutegravir activity was measured for 705 raltegravir resistant recombinant isolates from clinical practice; 93,9 % (662/705) of the isolates had a dolutegravir FC ≤10 and 1,8 % had a DTG FC > 25. Mutants with Y143 and N155 pathway had mean FCs of 1,2 and 1,5, respectively, while Q148 + 1 mutant and Q148 + ≥ 2 mutants mean FCs were 4,8 and 6,0, respectively.

Rilpivirine retained sensitivity (FC ≤ BCO) against 62 % of 4786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Effects on Electrocardiogram:

In a randomised, placebo-controlled, cross-over trial, 42 healthy subjects received single dose oral administrations of placebo, dolutegravir 250 mg suspension (exposures approximately 3-fold of the 50 mg once-daily dose at steady state), and moxifloxacin (400 mg, active control) in random sequence. Dolutegravir did not prolong the QTc interval for 24 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1,99 msec (1-sided 95 % upper CI: 4,53 msec).

The effect of rilpivirine at the recommended dose of 25 mg once 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. Rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg and 300 mg once daily of rilpivirine were studied in healthy adults, 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 and 300 mg once daily resulted in a mean C_{max} approximately 2,6-fold and 6,7-fold, respectively, higher than the mean steady-state C_{max} observed with the 25 mg once daily dose of rilpivirine.

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 modest decrease in CrCl and increase in serum creatinine, were observed with dolutegravir within the first week of treatment, consistent with that seen in clinical studies. Dolutegravir at both doses had no significant effect on the GFR or the ERPF. These data support *in vitro* studies which 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:

The dolutegravir/rilpivirine tablet is bioequivalent to dolutegravir 50 mg tablets and rilpivirine 25 mg tablets administered together with a meal.

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 variability CVb % for AUC and C_{max} ranged from ~20 to 40 % and for trough plasma concentrations from 30 to 65 % across studies. The between-subject PK variability of DTG was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw %) is lower than between-subject variability.

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

Absorption:

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of 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 systemic exposure appears dose proportional from 25 mg to 50 mg.

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours.

The absolute bioavailability of dolutegravir or rilpivirine has not been established.

Effect of Food:

Dolutegravir/rilpivirine tablet should be taken with a meal. When the dolutegravir/rilpivirine tablet was taken with a meal, the absorption of both dolutegravir and rilpivirine was increased. Moderate and high fat meals increased the dolutegravir $AUC_{(0-\infty)}$ by approximately 87 % and C_{max} by approximately 75 %. Rilpivirine $AUC_{(0-\infty)}$ was increased by 57 % and 72 % and C_{max} by 89 % and 117 %, with moderate and high fat meals respectively, compared to fasted conditions.

Food increases the extent and slows the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ 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 exposure to rilpivirine was approximately 40 % lower when 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 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) 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 12 treatment-naïve subjects receiving a regimen of dolutegravir plus abacavir/lamivudine for 16 weeks, dolutegravir concentration in CSF averaged 15,4 ng/ml at Week 2 and 12,6 ng/ml at Week 16, ranging from 3,7 to 23,2 ng/ml (comparable to unbound plasma concentration). The CSF:plasma concentration ratio of DTG ranged from 0,11 to 2,04. Dolutegravir concentrations in CSF exceeded the IC_{50}, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,2 log after 2 weeks and 3,4 log after 16 weeks of therapy.

Rilpivirine is highly bound (approximately 99,7 %) 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 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).

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

Elimination:

Dolutegravir has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 0,56 ℓ/hr. 53 % of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed dolutegravir or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. 31 % 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 has a terminal elimination half-life of approximately 45 hours. After single dose oral administration of 14C-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 total dose) were detected in urine.

Special patient populations:

Children: Dolutegravir/rilpivirine tablet has not been studied in the paediatric population.

Elderly: Population pharmacokinetic analysis using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir or rilpivirine exposures. Pharmacokinetic data in subjects > 65 years old are limited.

Renal impairment:

No dosage adjustment is necessary for patients with 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 (CrCl < 30 ml/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCl < 30 ml/min) and matching healthy subjects were observed. There is limited information on dolutegravir in patients on dialysis, though differences in exposure are not expected.

The pharmacokinetics of rilpivirine have 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 and rilpivirine are primarily metabolised and eliminated by the liver. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score A or B).

In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups.

In a study comparing 8 patients with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child-Pugh score B) to 8 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.

The effect of severe hepatic impairment (Child-Pugh score C) on the pharmacokinetics of dolutegravir or rilpivirine have not been studied.

Polymorphisms in Metabolising Enzymes:

There is no evidence that common polymorphisms in medicine 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.

Rilpivirine pharmacokinetics are not anticipated to be impacted by polymorphisms in drug metabolising enzymes.

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 or rilpivirine. Subjects with hepatitis B co-infection were excluded from studies with dolutegravir/rilpivirine tablet.

Pregnancy and Postpartum:

The exposure to total rilpivirine after intake of rilpivirine 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2nd and 3rd trimester) compared with postpartum. The decrease in unbound (active) rilpivirine pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total rilpivirine.

In women receiving rilpivirine 25 mg once daily during the 2nd trimester of pregnancy, mean intra-individual values for total rilpivirine C_{max}, AUC_{24h} and C_{min} values were, respectively, 21 %, 29 % and 35 % lower as compared to postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h} and C_{min} values were, respectively, 20 %, 31 % and 42 % lower as compared to postpartum.

There are no pharmacokinetic data on the use of dolutegravir in pregnancy.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Croscarmellose sodium, magnesium stearate, D-mannitol, lactose monohydrate, microcrystalline cellulose, polysorbate 20, povidone K30, povidone K29/32, sodium starch glycolate, sodium stearyl fumerate and silicified microcrystalline cellulose.

The film-coat contains, polyvinyl alcohol, titanium dioxide, macrogel/PEG, talc, yellow and red iron oxide.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 months

6.4 Special precautions for storage:

Store at or below 30 ºC.

Store in the original package to protect from moisture.

Keep the bottle tightly closed. Do not remove the desiccant.

6.5 Nature and contents of container:

A carton containing a white HDPE (high density polyethylene) bottle closed with polypropylene child-resistant closure. Each bottle contains 30 film-coated tablets and a desiccant.

6.6 Special precautions for disposal:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

52/20.2.8/0990

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