JULUCA

Dolutegravir/Rilpivirine

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

CLINICAL INFORMATION

Indications

JULUCA 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) without known or suspected resistance to either antiretroviral component.

Dosage and Administration

Pharmaceutical Form: Film-coated tablets.

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

If the patient misses a dose of *JULUCA*, 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 are available where dose adjustment or discontinuation of one of the individual components is indicated (*see Interactions*). In these cases the physician should refer to the individual product information.

Adults

The recommended dose of *JULUCA* in adults is one tablet once daily taken orally with a meal.

Adolescents and Children

JULUCA is not recommended in pediatric patients below 18 years of age due to insufficient safety and efficacy data.

Elderly

No dose adjustment of *JULUCA* is required in elderly patients. There are limited data available on the use of *JULUCA* in patients aged 65 years and over (*see Pharmacokinetics – Special Patient Populations*).

Renal impairment

No dosage adjustment of *JULUCA* is required in patients with renal impairment (*see Pharmacokinetics — Special Patient Populations*).

Hepatic impairment

No dosage adjustment of *JULUCA* is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). *JULUCA* has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (*see Pharmacokinetics – Special Patient Populations*).

Contraindications

JULUCA is contraindicated in patients with known hypersensitivity to dolutegravir or rilpivirine or to any excipients of *JULUCA*.

JULUCA is contraindicated in combination with the following *(see Interactions*):

- products with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to antiarrhythmic agents dofetilide or pilsicainide, or the potassium channel blocker fampridine (also known as dalfampridine).
- anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, 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*).

Warnings and Precautions

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue *JULUCA* and other suspect agents 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 *JULUCA* or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Interactions with medicinal products:

Caution should be given to prescribing *JULUCA* with medicinal products that may reduce the exposure of dolutegravir or rilpivirine (*see Interactions*).

Opportunistic infections:

Patients receiving *JULUCA* 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 physicians experienced in the treatment of these associated HIV diseases.

Interactions

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

Effect of *JULUCA* on the Pharmacokinetics of Other Agents

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

Dolutegravir is not expected to affect the pharmacokinetics of drugs 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 drugs 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 drug 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). 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 drugs 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 drug interactions via inhibition of OAT transporters.

Effect of Rilpivirine on the Pharmacokinetics of Other Agents

Rilpivirine at a dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.

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

Interactions with medicinal products are listed in Table 1.

Effect of Other Agents on the Pharmacokinetics of *JULUCA*

Effect of Other Agents 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 drugs 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 drugs 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 drugs that solely modulate these transporters are not expected to affect dolutegravir plasma concentration.

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

Interactions with medicinal products are listed in Table 1.

Effect of Other Agents on the Pharmacokinetics of Rilpivirine

Rilpivirine is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (*see Pharmacokinetics*). Co-administration of rilpivirine with medicinal products 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 medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

Co-administration of rilpivirine with medicinal products that increase gastric pH may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of rilpivirine.

Interactions with medicinal products are listed in Table 1.

QT prolonging drugs

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products 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 Pharmacodynamics – Effects on Electrocardiogram*). *JULUCA* should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

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

Table 1 Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug***	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: Delavirdine,	Dolutegravir ↓ Rilpivirine ↓ (↑ with delavirdine)	Co-administration of *JULUCA* with another NNRTI is not recommended.

Efavirenz, Etravirine, Nevirapine		
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 *JULUCA* with tipranavir/ritonavir is not recommended.
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.
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%	Tenofovir did not change dolutegravir/rilpivirine plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.

	C_{max} ↑ 19% C_{min} ↑ 24 %	
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 *JULUCA* is necessary. Didanosine should be administered on an empty stomach at least 2 hours before or 4 hours after *JULUCA* (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 Agents		
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 Agents		
Dofetilide	Effect of dolutegravir:	Co-administration of *JULUCA* with dofetilide or pilsicainide is

Pilsicainide	Dofetilide ↑ Pilsicainide ↑	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; co-administration has not been studied. Fampridine co-administration with *JULUCA* is contraindicated.
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 *JULUCA* with these metabolic inducers is contraindicated.
Herbal products: St. John's wort (*Hypericum perforatum*)	Dolutegravir ↓ Rilpivirine ↓	Co-administration of *JULUCA* with products containing St. John's wort may significantly decrease dolutegravir/rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of *JULUCA* with products containing St. John's wort is contraindicated.
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 *JULUCA* with proton pump inhibitors is contraindicated.
H_2-Receptor Antagonists: Famotidine†	Dolutegravir ↔ Rilpivirine:	H2-receptor antagonists may significantly decrease rilpivirine plasma concentrations. *JULUCA*

Cimetidine Nizatidine Ranitidine	Famotidine taken 12 hrs before Rilpivirine AUC ↓ 9% C_{max} ↔ C_{min} NA Famotidine taken 2 hrs before Rilpivirine AUC ↓ 76% C_{max} ↓ 85% C_{min} NA Famotidine taken 4 hrs after Rilpivirine AUC ↑ 13% C_{max} ↑ 21% C_{min} NA	should be administered at least 4 hours before or at least 12 hours after H2-receptor antagonists.
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. *JULUCA* 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%	*JULUCA* 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 ↔	Co-administration of *JULUCA* may increase metformin plasma concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of *JULUCA* with metformin, to maintain glycaemic control.

	AUC ↔ C_{max} ↔ C_{min} NA	
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 *JULUCA* with rifampicin or rifapentine is contraindicated.
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 *JULUCA*.
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 *JULUCA* with dexamethasone is contraindicated, except for single dose use. Alternatives should be considered, particularly for long-term use.
Oral contraceptives (Ethinyl estradiol (EE) and	Effect of dolutegravir: EE ↔ AUC ↑ 3%	Dolutegravir/rilpivirine did not change ethinyl estradiol and norelgestromin/norethindrone plasma

Norelgestromin (NGMN)) Norethindrone	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} ↔	concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with *JULUCA*.
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 *JULUCA*. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
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.
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)	No dose adjustment is necessary.

	AUC ↔ C_{max} NA C_{min} ↔	

* Where pharmacokinetic parameters are presented, the interaction between dolutegravir and/or rilpivirine and the drug was evaluated in a clinical study. All other drug-drug 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 drug.

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

Pregnancy and Lactation

Fertility

There are no data on the effects of dolutegravir and/or rilpivirine on human male or female fertility. Animal studies indicate no effects of dolutegravir or rilpivirine on male or female fertility (*see Non-Clinical information).*

Pregnancy

JULUCA should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. Women of childbearing potential (WOCBP) should be informed about the potential risk of neural tube defects with dolutegravir and counselled about the use of effective contraception. It is recommended that pregnancy testing is conducted prior to initiation of *JULUCA*. If there are plans to become pregnant, or if pregnancy is confirmed within the first trimester while on *JULUCA*, the risks and benefits of continuing *JULUCA* versus switching to another antiretroviral regimen should be discussed with the patient. Factors to consider should include feasibility of switching, tolerability, ability to maintain viral suppression, actual gestational age, risk of transmission to the infant and the available data around the potential risk of neural tube defects and other pregnancy outcomes for dolutegravir and alternative antiretroviral drugs.

In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was identified with exposure to dolutegravir compared to non-dolutegravir-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.03, 0.30).

In the same study, an increased risk of neural tube defects was not identified in women who started dolutegravir during pregnancy. Two out of 4,448 deliveries (0.04%) to

mothers who started dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-dolutegravir-containing regimens during pregnancy.

A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As most neural tube defects occur within the first 4 weeks of foetal development (approximately 6 weeks after the last menstrual period) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Data analysed to date from other sources including the Antiretroviral Pregnancy Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with dolutegravir.

More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

In animal reproductive toxicity studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified (*see Non-Clinical information*).

Dolutegravir and rilpivirine use during pregnancy have been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 600 and 610 women, respectively (as of July 2019). Available human data from the APR do not show an increased risk of major birth defects for dolutegravir or rilpivirine compared to the background rate (*see Clinical Studies*).

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). Virologic response was preserved throughout the trial period. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults.

Studies in rats and rabbits with rilpivirine have shown no evidence of relevant embryonic or foetal toxicity, effect on reproductive function, or teratogenicity (*see Non-Clinical information*).

Lactation

Health experts recommend that where possible HIV infected women do not breast feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

Dolutegravir is excreted in human milk in small amounts. 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.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *JULUCA* on driving performance or the ability to operate machinery. The clinical status of the patient and the adverse event profile of *JULUCA* should be borne in mind when considering the patient's ability to drive or operate machinery.

Adverse Reactions

Clinical trial data

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

Adverse reactions are adverse events that were considered to be reasonably associated with the use of a drug based on the comprehensive assessment of the available adverse event information. A causal relationship cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse drug reactions (ADRs) identified in an analysis of pooled data from Phase 2b and Phase 3 clinical studies of the individual components 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 pooled data from Phase 3 clinical trials (SWORD-1 and SWORD-2) 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 the SWORD-1 and SWORD-2 trials were diarrhoea and headache.

Table 2 Adverse Reactions with the Individual Components of *JULUCA*

System	Frequency*	DTG	RPV
Immune system disorders	Uncommon	Hypersensitivity (*see Warnings and Precautions*) 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	Headache	
	Common	Dizziness	Headache Dizziness
	Uncommon		Somnolence
Gastrointestinal disorders	Very common	Nausea Diarrhoea	
	Common	Abdominal pain Vomiting Flatulence Upper abdominal pain Abdominal discomfort	Abdominal pain Nausea Vomiting
	Uncommon		Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis	
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 Pharmacodynamics – 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 Pharmacokinetics – 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.

Paediatric population

There are no clinical study data with dolutegravir plus rilpivirine in the paediatric population.

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 adverse reactions included from clinical trial data, below are adverse reactions 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:** Uncommon: arthralgia, myalgia
- **Investigations:** Common: weight increased.

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

- **Hepatobiliary disorders:** Rare: acute hepatic failure

Overdose

Symptoms and signs

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

Treatment

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

There is no specific treatment for overdose with *JULUCA*. If overdose occurs, the patient should be treated supportively with appropriate monitoring, vital signs, ECG (QT interval), 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. 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 drugs 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 drugs 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-drug 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

The number of subjects who met the protocol-defined confirmed virologic withdrawal (CVW) criteria was low across the pooled SWORD-1 and SWORD-2 studies.

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=0.8) 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 to 1,018 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.

In the pooled analyses from Week 48 through Week 148, nine additional subjects receiving dolutegravir plus rilpivirine met CVW criteria at any time. Of the eight who had resistance testing results available, six (described below) had postbaseline results or resistance associated substitutions (NNRTI and/or INI).

- *Subjects receiving dolutegravir plus rilpivirine from study start who met CVW criteria*: At Week 88, one subject had the NNRTI-resistance-associated substitution mixture E138E/A with no decreased susceptibility to rilpivirine (FC = 1.6), and one subject had K103N with rilpivirine FC = 5.2. Neither subject had INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir. At Week 100, one subject with baseline NNRTI-resistance-associated substitutions K101E, E138A had M230M/L in addition to K101E and E138A with rilpivirine FC = 31. Integrase resistance testing failed at virologic failure. At Week 112, one subject had M230M/L mixture with rilpivirine FC = 2, and INSTI polymorphic substitutions E157Q, G193E, T97T/A at baseline and

E157Q, G193E at virologic failure with no decreased susceptibility to dolutegravir (FC = 1.5).

- *Subjects receiving dolutegravir plus rilpivirine from Week 52 who met CVW criteria:* At Week 64, one subject had integrase substitutions N155H, G163G/R at baseline and only polymorphic integrase V151I/V mixture at virologic failure, and no NNRTI resistance. Integrase phenotype assay failed, and HIV-1 RNA was less than 50 copies per mL at withdrawal visit. At Week 136, one subject had NNRTI-resistance-associated substitutions E138A and L100L/I with rilpivirine FC = 4.1 and integrase resistance testing failed at virologic failure.

Treatment-naïve HIV-1 infected subjects on Dolutegravir: No integrase-resistant mutations or treatment-emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment–naive studies.

Treatment-naïve HIV-1 infected subjects on Rilpivirine: In a Week 96 pooled analyses of virologic failures with baseline viral load ≤100,000 copies/mL and resistance to rilpivirine (n = 5), subjects had cross-resistance to efavirenz (n = 3), etravirine (n = 4), and nevirapine (n = 1).

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.

Considering all of the available in vitro and in vivo data, the following amino acid substitutions, when present at baseline, are likely to affect the activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, or M230L.

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 was 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 GFR or ERPF. These data support in vitro studies which suggest that the small increases in creatinine observed in clinical studies are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Effects on Bone

Mean bone mineral density (BMD) significantly increased from Baseline to Week 48 in subjects who switched to dolutegravir plus rilpivirine (1.34% total hip and 1.46% lumbar spine) compared with those who continued on treatment with a TDF-containing

antiretroviral regimen (0.05% total hip and 0.15% lumbar spine; p = 0.014 and p = 0.039, respectively) in a DEXA substudy.

Pharmacokinetics

The *JULUCA* 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 CVb% for AUC and C_{max} ranged from ~20 to 40% and $C\tau$ from 30 to 65% across studies. The between-subject PK variability of 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

JULUCA should be taken with a meal. When *JULUCA* 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). 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.

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

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 metabolized 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 drug 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. 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 drug 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 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

JULUCA 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 drug 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 metabolized 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 Drug Metabolising Enzymes

There is no evidence that common polymorphisms in drug 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.

Gender

Population pharmacokinetic analyses revealed no clinically relevant effect of gender on the exposure of dolutegravir.

No clinically relevant differences in the pharmacokinetics of rilpivirine have been observed between men and women.

Race

Population pharmacokinetic analyses revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese subjects appear similar to observed parameters in Western (US) subjects.

Population pharmacokinetic analyses of rilpivirine in HIV-infected patients indicated that race had no clinically relevant effect on the exposure to rilpivirine.

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 *JULUCA*.

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.

Clinical Studies

The efficacy of *JULUCA* is supported by data from 2 randomised, open-label, controlled trials (SWORD-1 [201636] and SWORD-2 [201637]) in virologically suppressed patients switching from their current antiretroviral regimen (CAR) to dolutegravir plus rilpivirine.

SWORD-1 and SWORD-2 are identical 148-week, Phase III, randomised, multicenter, parallel-group, non-inferiority studies. A total of 1,024 adult HIV-1 infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 NRTIs plus either an INI, an NNRTI, or a PI) received treatment in the studies. Subjects were randomised 1:1 to continue their CAR or be switched to a two-drug regimen dolutegravir plus rilpivirine administered once daily. At Week 52, subjects who were originally assigned to continue their CAR and remained virologically suppressed switched to dolutegravir plus rilpivirine. The primary efficacy endpoint for the SWORD studies was the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm for the ITT-E population).

At baseline, in the pooled analysis, the median age of subjects was 43 years, 22% female, 20% non-white, 11% were CDC Class C (AIDS), and 11% had CD4+ cell count less than 350 cells per mm3; these characteristics were similar between treatment arms. In the pooled analysis, 54%, 26%, and 20% of subjects were receiving an NNRTI, PI, or INI (respectively) as their baseline third treatment agent class prior to randomisation and was similar between treatment arms.

The pooled primary analysis demonstrated that dolutegravir plus rilpivirine is non-inferior to CAR, with 95% of subjects in both arms achieving the primary endpoint of

<50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm (Table 3).

The primary endpoint and other outcomes (including outcomes by key baseline covariates) for the pooled SWORD-1 and SWORD-2 studies are shown in Table 3.

Table 3 Virologic Outcomes of Randomised Treatment at Week 48 (Snapshot algorithm)

	SWORD-1 and SWORD-2 Pooled Data	
	DTG + RPV N=513	**CAR N=511**
HIV-1 RNA <50 copies/mL	95%	95%
Treatment Difference*	-0.2 (-3.0, 2.5)	
Virologic non response†	<1%	1%
Reasons		
Data in window not <50 copies/mL	0	<1%
Discontinued for lack of efficacy	<1%	<1%
Discontinued for other reasons while not <50 copies/mL	<1%	<1%
Change in ART	0	<1%
No virologic data at Week 48 window	5%	4%
Reasons		
Discontinued study/study drug due to adverse event or death	3%	<1%
Discontinued study/study drug for other reasons	1%	3%
Missing data during window but on study	0	<1%
HIV-1 RNA <50 copies/mL by baseline covariates	n/N (%)	n/N (%)
Baseline CD4+ (cells/ mm^3)		
<350	51 / 58 (88%)	46 / 52 (88%)
≥350	435 / 455 (96%)	439 / 459 (96%)
Baseline Third Treatment Agent Class		
INSTI	99 / 105 (94%)	92 / 97 (95%)
NNRTI	263 / 275 (96%)	265 / 278 (95%)
PI	124 / 133 (93%)	128 / 136 (94%)
Gender		
Male	375 / 393 (95%)	387 / 403 (96%)
Female	111 / 120 (93%)	98 / 108 (91%)
Race		
White	395 / 421 (94%)	380 / 400 (95%)
African-America/African Heritage/Other	91 / 92 (99%)	105 / 111 (95%)
Age (years)		
<50	350 / 366 (96%)	348 / 369 (94%)
≥50	136 / 147 (93%)	137 / 142 (96%)

* Adjusted for baseline stratification factors and assessed using a non-inferiority margin of -8%.

† Non-inferiority of DTG + RPV to CAR in the proportion of subjects classified as virologic non-responders was demonstrated using a non-inferiority margin of 4%. Adjusted difference (95% CI) -0.6 (-1.7, 0.6).

N = Number of subjects in each treatment group

CAR = current antiretroviral regimen; DTG+RPV = dolutegravir plus rilpivirine; INSTI = Integrase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease Inhibitor

At Week 148 in the pooled SWORD-1 and SWORD-2 trials, 84% of subjects who received dolutegravir plus rilpivirine as of study start had plasma HIV-1 RNA < 50 copies/mL based on the Snapshot algorithm. In subjects who initially remained on their CAR and switched to dolutegravir plus rilpivirine at Week 52, 90% had plasma HIV-1 RNA < 50 copies/mL at Week 148 based on the Snapshot algorithm, which was comparable to the response rate (89%) observed at Week 100 (similar exposure duration) in subjects receiving dolutegravir plus rilpivirine as of study start.

Antiretroviral Pregnancy Registry

The APR has received reports of over 600 exposures to dolutegravir during pregnancy resulting in live births, as of July 2019. These consist of over 370 exposures during the first trimester, over 230 exposures during the second/third trimester and included 12 and 9 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to dolutegravir in the first trimester was 3.2% (1.7%, 5.5%) and in the second/third trimester, 3.8% (1.7%, 7.0%).

The APR has received reports of over 610 exposures to rilpivirine during pregnancy resulting in live birth, as of July 2019. These consist of over 420 exposures during the first trimester, over 190 exposures during the second/third trimester and included 6 and 3 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to rilpivirine in the first trimester was 1.4% (0.5, 3.0%) and in the second/third trimester, 1.6% (0.3, 4.5%).

The available data from the APR shows no significant increase in risk of major birth defects for dolutegravir or rilpivirine compared to the background rates in the two population based surveillance systems (Metropolitan Atlanta Congenital Defects Program with defects of 2.72 per 100 live births and the Texas Birth Defects Registry with 4.17 per 100 live births).

Children

There are no clinical study data with *JULUCA* in the paediatric population.

Non-Clinical Information

Carcinogenesis/mutagenesis

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

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1,500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine

did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent-specific, associated with liver enzyme induction. A similar mechanism does not exist in humans; hence, these tumours are not relevant for humans. The follicular cell findings are considered to be rat-specific associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily).

Rilpivirine has tested negative in the in vitro Ames reverse mutation assay, in vitro chromosomal aberration assay in human lymphocyte and in vitro clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. Rilpivirine did not induce chromosomal damage in the in vivo micronucleus test in mice.

Reproductive Toxicology

Fertility

Dolutegravir did not affect male or female fertility in rats at doses up to 1,000 mg/kg/day, the highest dose tested (33 times the 50 mg human clinical exposure based on AUC).

In rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day (dose that showed maternal toxicity). A dose associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily).

Pregnancy

Oral administration of dolutegravir to pregnant rats at doses up to 1,000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (37.9 times the 50 mg human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.56 times the 50 mg human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was observed at 1,000 mg/kg (0.56 times the 50 mg human clinical exposure based on AUC).

Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function with rilpivirine. There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. In a pre- and postnatal development assessment in rats, rilpivirine had no effect on development of offspring during lactation or post weaning when the mothers were dosed up to 400 mg/kg/day.

Animal toxicology and/or pharmacology

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 30 and 1.2 times the 50 mg human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local drug administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 30 times the human mg/kg equivalent dose (based on 50 kg human), and 11 times the human mg/m^2 equivalent dose for a total daily clinical dose of 50 mg.

Animal toxicology studies have been conducted with rilpivirine in mice, rats, rabbits, dogs and cynomolgus monkeys. The target organs and systems of toxicity were the adrenal cortex and the associated steroid biosynthesis (mouse, rat, dog, cynomolgus monkey), the reproductive organs (female mouse, male and female dog), the liver (mouse, rat, dog), the thyroid and pituitary gland (rat), the kidney (mouse, dog), the hematopoietic system (mouse, rat, dog), and the coagulation system (rat).

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet core:

D-mannitol
Magnesium stearate
Microcrystalline cellulose
Povidone K29/32
Sodium starch glycolate
Sodium stearyl fumarate
Lactose monohdrate
Croscarmellose sodium
Povidone K30
Polysorbate 20
Silicified microcrystalline cellulose

Tablet coating:

Opadry II Pink 85F240164 containing:
Polyvinyl Alcohol- Part Hydrolysed
Titanium dioxide
Macrogol/PEG
Talc
Iron oxide yellow
Iron oxide red

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Store in the original package to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant.

Nature and Contents of Container

JULUCA tablets are supplied in white HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures. Each bottle contains a desiccant.

Incompatibilities

No incompatabilities have been identified.

Use and Handling

There are no special requirements for use or handling of this product.

Not all presentations are available in every country.

GSK is committed to the effective collection and management of human safety information relating to our products and we encourage health care professionals to report adverse events to us via phone call to +254-20-6933200 or email us on ke.safety@gsk.com

Full prescribing information is available on request from GlaxoSmithKline, P.O Box 78392-00507 Nairobi, Kenya or via our Healthcare Professionals Website www.gskpro.com

Full Prescribing Information prepared in September 2022 based on GDSv09 dated 10 August 2022.

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