AUSTRALIAN PRODUCT INFORMATION

JULUCA (dolutegravir/rilpivirine fixed-dose combination) film-coated tablets

1 NAME OF THE MEDICINE

Dolutegravir (as dolutegravir sodium) and rilpivirine (as rilpivirine hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

JULUCA film-coated tablets contain 50 mg of dolutegravir (as dolutegravir sodium) and 25 mg of rilpivirine (as rilpivirine hydrochloride).

Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water. The partition coefficient (log P) for dolutegravir sodium is 2.2 and the pKa is 8.2.

Rilpivirine hydrochloride is a white to off-white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range, its pKa is 5.6 (pyrimidine moiety) and log P between 1-octanol and a phosphate solution (pH 7.0) is 4.86 (at 21°C).

JULUCA tablets also contain mannitol and lactose monohydrate.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

JULUCA (dolutegravir/rilpivirine) is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor (see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

JULUCA 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 Section 4.5

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 paediatric patients below 18 years of age due to insufficient safety and efficacy data.

Elderly
There are limited data available on the use of JULUCA in patients aged 65 years and over. Caution should be exercised in administration of JULUCA in elderly patients reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Renal impairment
No dosage adjustment is required in patients with mild or moderate renal impairment. In patients with severe or end stage renal disease, the combination of JULUCA with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. No data are available in subjects receiving dialysis. (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Dolutegravir has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when JULUCA is co-administered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance.

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); therefore, JULUCA is not recommended in these patients (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Women of child-bearing potential and pregnancy
The safety and efficacy of JULUCA in pregnancy have not yet been established. No recommendations for dose adjustments can be made for JULUCA. Therefore, use of JULUCA during pregnancy is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Pregnancy, Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in pregnancy and Section 5.2. PHARMACOKINETIC PROPERTIES, Special patient populations).

4.3 CONTRAINDICATIONS

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

JULUCA is contraindicated in combination with the following (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

- 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*).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions
Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterised 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.

Hepatotoxicity
Hepatic adverse events have been reported in patients receiving a dolutegravir-or rilpivirine containing regimen. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations. Additionally, in some patients receiving dolutegravir containing regimens, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity including elevated serum liver biochemistries and hepatitis have also been reported in patients receiving a dolutegravir-or rilpivirine-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to acute liver failure has been reported with dolutegravir-containing products, including liver transplant with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

Patients with hepatitis B or C
No clinical data are available in patients with hepatitis B co-infection. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus. Limited data is available in patients with hepatitis C co-infection. A higher incidence of liver chemistry elevations (Grade 1) were observed in patients treated with dolutegravir and rilpivirine co-infected with hepatitis C compared to those who were not co-

infected. Monitoring of liver function is recommended in patients with hepatitis B and/or C co-infection.

Immune Reactivation Syndrome
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Depressive Disorders
Depressive disorders (including depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, and suicidal ideation) have been reported with rilpivirine or dolutegravir. Promptly evaluate patients with severe depressive symptoms to assess whether the symptoms are related to JULUCA and to determine whether the risks of continued therapy outweigh the benefits.

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.

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.

Serum lipids and blood glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Pregnancy
The safety and efficacy of JULUCA in pregnancy have not yet been established. In phase 3 studies, lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure. No recommendations for dose adjustments can be made for JULUCA. Therefore, use of JULUCA during pregnancy is not recommended (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION and Section 5.2. PHARMACOKINETIC PROPERTIES, Special patient populations).

Use in hepatic impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Use in renal impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Use in the elderly
Clinical trials of JULUCA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in administration of JULUCA in elderly patients reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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

Effects on laboratory tests

Table 1 -. Selected laboratory abnormalities (Grades 2 ,3 and 4; week 48 pooled analyses) in SWORD-1 and SWORD-2 Trials

Laboratory Parameter Preferred Term	Dolutegravir plus Rilpivirine (n = 513)	Current Antiretroviral Regimen (n = 511)
ALT		
Grade 2 (>2.5-5.0 x ULN)	2%	<1%
Grade 3 to 4 (>5.0 x ULN)	<1%	<1%
AST		
Grade 2 (>2.5-5.0 x ULN)	<1%	2%
Grade 3 to 4 (>5.0 x ULN)	<1%	<1%
Total Bilirubin		
Grade 2 (1.6-2.5 x ULN)	2%	4%
Grade 3 to 4 (>2.5 x ULN)	0	3%
Creatine kinase		
Grade 2 (6.0-9.9 x ULN)	<1%	<1%
Grade 3 to 4 (≥10.0 x ULN)	1%	2%
Hyperglycemia		
Grade 2 (126-250 mg/dL)	4%	5%
Grade 3 to 4 (>250 mg/dL)	<1%	<1%
Lipase		
Grade 2 (>1.5-3.0 x ULN)	5%	5%
Grade 3 to 4 (>3.0 x ULN)	2%	2%

ULN = Upper limit of normal.

In the SWORD studies 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 PHARMACODYNAMIC PROPERTIES, 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 PHARMACOKINETIC PROPERTIES, 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (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. *In vivo* dolutegravir increases plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE1 (for example dofetilide, pilsicainide, fampridine or metformin) (see Table 2). Given the *in vivo* exposure, dolutegravir has a low potential to affect the transport of MATE2-K substrates *in vivo.*

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (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.

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, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MRP2 or MRP4. *In vitro,* dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

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.

Effect of rilpivirine on the pharmacokinetics of other agents
In vitro, rilpivirine inhibited the MATE2-K transporter (IC50 < 0.05 µM), and may slow the elimination of MATE2-K substrates in vivo.

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 2.

Effect of other agents on the pharmacokinetics of dolutegravir/rilpivirine

Effect of other agents on the pharmacokinetics of dolutegravir
Dolutegravir is metabolised by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, Pgp, and BCRP *in vitro;* therefore drugs that induce those enzymes or transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 2).

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 2.

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 Section 5.2 PHARMACOKINETIC PROPERTIES). 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 2.

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 Section 5.1 PHARMACODYNAMIC PROPERTIES). 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 2. The 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 2: 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, Efavirenz, Etravirine, Nevirapine	Dolutegravir ↓ Rilpivirine ↓ (↑ with delavirdine)	Co-administration of JULUCA with another NNRTI is not recommended.
Protease Inhibitor (PI): Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% $C\tau$ ↑ 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% $C\tau$ ↑ 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% $C\tau$ ↓ 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% $C\tau$ ↓ 49% FPV ↔ RTV ↔ Rilpivirine ↑	Fosamprenavir/ritonavir may increase rilpivirine plasma concentrations and decrease dolutegravir concentrations. No dose adjustment is necessary.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug***	**Clinical Comment**
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} ↔ $C\tau$ ↓ 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% $C\tau$ ↓ 38% DRV ↔ RTV ↔ Rilpivirine ↑ AUC ↑ 130% C_{max} ↑ 79% C_{min} ↑ 178%	Darunavir/ritonavir did not change dolutegravir plasma concentrations to a clinically relevant extent, whereas, concomitant use of rilpivirine with darunavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir disoproxil fumarate†	Dolutegravir ↔ AUC ↔ C_{max} ↓3% $C\tau$ ↓ 8% Effect of dolutegravir: Tenofovir ↔ AUC ↑ 12 % C_{max} ↑ 9% $C\tau$ ↑ 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.
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 ↑	No dose adjustment is necessary.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug*	Clinical Comment
	AUC ↑ 9% C_{max} ↑ 10% C_{min} ↑ 27%	
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 Pilsicainide	Effect of dolutegravir: Dofetilide ↑ Pilsicainide ↑	Co-administration of JULUCA with dofetilide or pilsicainide is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentrations.
Fampridine	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 JULUCA is contraindicated.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Effect of carbamazepine: Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% $C\tau$ ↓ 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.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug***	**Clinical Comment**
H_2-Receptor Antagonists: Famotidine† Cimetidine Nizatidine Ranitidine	Dolutegravir ↔ Rilpivirine: 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	H_2-receptor antagonists may significantly decrease rilpivirine plasma concentrations. JULUCA should be administered at least 4 hours before or at least 12 hours after H_2-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% C_{24} ↓ 39% Iron: Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 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 ↔ AUC ↔ C_{max} ↔ C_{min} NA	Co-administration of JULUCA may increase metformin plasma concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of JULUCA with metformin, to maintain glycaemic control.
Rifampicin† Rifapentine	Dolutegravir ↓ (by rifampicin) AUC ↓ 54% C_{max} ↓ 43% $C\tau$ ↓ 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 decreased the plasma concentrations of rilpivirine. During co-administration with

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug*	Clinical Comment
	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 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 Norelgestromin (NGMN)) Norethindrone	Effect of dolutegravir: EE ↔ AUC ↑ 3% C_{max} ↓ 1% $C\tau$ ↑ 2% Effect of dolutegravir: NGMN ↔ AUC ↓ 2% C_{max} ↓ 11% $C\tau$ ↓ 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 JULUCA.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% $C\tau$ ↓ 1% Effect of rilpivirine: Methadone ↓ AUC ↓ 16% C_{max} ↓ 14% $C\tau$ ↓ 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%	Azole antifungal agents may increase rilpivirine plasma concentrations. No dose adjustment is necessary.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug*	Clinical Comment
	Ketoconazole (by rilpivirine) AUC ↓ 24% C_{max} ↔ C_{min} ↓ 66%	
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) AUC ↔ C_{max} NA C_{min} ↔	No dose adjustment is necessary.

* 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, $C\tau$ = concentration at the end of dosing interval; NA = not assessed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effects of dolutegravir and/or rilpivirine on human male or female fertility. Dolutegravir did not affect male or female fertility in rats at doses up to 1,000 mg/kg/day, associated with an exposure level 33 times the clinical exposure based on AUC at the maximum recommended dose of 50 mg once daily (QD).

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

Use in pregnancy
(Category B1)

The safety and efficacy of JULUCA in pregnancy have not been established. Use of JULUCA during pregnancy is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

No studies on the effect on embryo-fetal development have been conducted with the dolutegravir/rilpivirine combination.

Summary

Data from two, ongoing birth outcome surveillance studies in Botswana and Eswatini which together include over 14,000 individuals evaluated during pregnancy show similar prevalence of neural tube defects among infants born to individuals taking dolutegravir at the time of conception compared to those born to individuals taking non-dolutegravir-containing regimens at conception or infants born to HIV-negative individuals.

There are insufficient human data on the use of JULUCA during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. However, available human data from the Antiretroviral Pregnancy Registry (APR) with the individual components of JULUCA do not indicate an increased risk of birth defects. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognised pregnancies is 2% to 4% and 15% to 20%, respectively.

Data on dolutegravir

The first interim analysis from an ongoing birth outcome surveillance study in Botswana identified an association between dolutegravir and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. A subsequent analysis was conducted based on a larger cohort from the birth outcome surveillance study in Botswana and included over 9,460 individuals exposed to dolutegravir at conception, 23,664 individuals exposed to non-dolutegravir-containing regimens, and 170,723 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.11% (95% CI: 0.05-0.19%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.11%, 95% CI: 0.07-0.16%), or to HIV-negative individuals (0.06%, 95% CI: 0.050.08%).

The Eswatini birth outcome surveillance study includes 9,743 individuals exposed to dolutegravir at conception, 1,838 individuals exposed to non-dolutegravir-containing regimens, and 32,259 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.08% (95% CI: 0.04-0.16%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.22%, 95% CI: 0.06-0.56%) or to HIV-negative individuals (0.08%, 95% CI: 0.06-0.12%). The observed prevalence of neural tube defects in infants delivered to individuals taking non-dolutegravir-containing regimens had a wide confidence interval due to low sample size.

Limitations of these birth outcome surveillance studies include insufficient data to determine if baseline characteristics were balanced between the study groups or to assess other factors such as the use of folic acid during the preconception or first trimester periods.

In animal reproductive toxicity studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified.

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 (38 times the human clinical exposure based on AUC at the maximum recommended dose of 50 mg QD).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation was associated with marked maternal toxicity but did not elicit developmental toxicity or teratogenicity in the offspring (0.56 times the clinical exposure based on AUC).

Dolutegravir readily crosses the placenta in humans. In pregnant women with HIV, 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.

There are insufficient human data on the use of JULUCA during pregnancy to definitively assess a drug-associated risk for birth defects. However, available human data from the APR with the individual components of JULUCA do not indicate an increased risk of birth defects. The exposure periods below refer to the trimester of earliest exposure. Only exposures with follow-up data are included.

The APR has received prospective reports of 1,506 exposures to dolutegravir-containing regimens during pregnancy resulting in live births, as of July 2023. These consist of 957 exposures during the first trimester, 549 exposures during the second/third trimester and included 32 and 29 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to dolutegravir-containing regimens in the first trimester was 3.3% (2.3%, 4.7%) and in the second/third trimester, 5.3% (3.6%, 7.5%).

In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%. The background risk for major birth defects for the treatment-indicated population is unknown.

Data on rilpivirine

Placental transfer of rilpivirine or its metabolites from dam to fetus was demonstrated in rats. Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function with rilpivirine. There was no clinically relevant 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.

The APR has received prospective reports of 928 exposures to rilpivirine-containing regimens during pregnancy resulting in live birth, as of July 2023. These consist of 712 exposures during the first trimester, 216 exposures during the second/third trimester and included 14 and 2 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to rilpivirine-containing regimens in the first trimester was 2.0% (1.1%, 3.3%) and in the second/third trimester, 0.9% (0.1%, 3.3%).

In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%. The background risk for major birth defects for the treatment-indicated population is unknown.

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.

Use in 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. In nonclinical studies, rilpivirine was detected in the plasma of suckling rats following maternal dosing.

4.7 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 JULUCA should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

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

The safety assessment of JULUCA in HIV-1-infected, virologically suppressed subjects switching from their current antiretroviral regimen to dolutegravir plus rilpivirine is based on the pooled primary Week 48 analyses of data from 2 identical, international, multicentre, open-label trials, SWORD-1 and SWORD-2 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product. A causal relationship does not necessarily exist between an AE and the medicinal product, but is at least suspected. An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended and for which a causal relationship is at least a reasonable possibility and cannot be ruled out.

Table 3: Summary of adverse events reported in ≥3% of subjects in any treatment group by overall frequency (week 48 pooled analysis)

Preferred Term	Dolutegravir plus Rilpivirine N=513 n(%)	Current Antiretroviral Regimen N=511 n(%)
Any event	**395 (77%)**	**364 (71%)**
Nasopharyngitis	49 (10%)	50 (10%)
Headache	41 (8%)	23 (5%)
Diarrhoea	32 (6%)	27 (5%)
Upper respiratory tract infection	24 (5%)	37 (7%)
Bronchitis	23 (4%)	15 (3%)
Arthralgia	21 (4%)	9 (2%)
Insomnia	17 (3%)	10 (2%)
Depression	17 (3%)	6 (1%)
Gastroenteritis	16 (3%)	10 (2%)
Dyspepsia	16 (3%)	9 (2%)
Sinusitis	16 (3%)	7 (1%)
Back pain	15 (3%)	31 (6%)
Dizziness	15 (3%)	1 (<1%)
Influenza	14 (3%)	17 (3%)
Asthenia	14 (3%)	12 (2%)

Preferred Term	Dolutegravir plus Rilpivirine N=513 n(%)	Current Antiretroviral Regimen N=511 n(%)
Abdominal pain upper	13 (3%)	7 (1%)
Pain in extremity	13 (3%)	6 (1%)
Constipation	13 (3%)	2 (<1%)
Flatulence	13 (3%)	0
Syphilis	10 (2%)	15 (3%)

The majority of adverse events reported during treatment with dolutegravir plus rilpivirine (DTG+RPV) or current antiretroviral regimen (CAR) were Grade 1 (DTG+ RPV 48%, CAR 48%) or Grade 2 (DTG +RPV 23%, CAR 20%) in severity. Grade 3 or 4 adverse events were reported in 5% and <1% of patients receiving DTG + RPV, and 3% and <1% of patients receiving treatment with CAR.

There were no treatment-emergent adverse drug reactions (ADRs) (Grades 2 to 4) with an incidence of at least 2% in either treatment arm. ADRs (all Grades) observed in at least 1% of subjects in either treatment arm of the pooled analysis of the SWORD-1 and SWORD-2 trials are provided in Table 4.

Table 4: Treatment-emergent adverse drug reactions (Grades 1 to 4) and at least 1% frequency in virologically suppressed subjects (week 48 pooled analyses)

System Organ Class/ Preferred Term	Dolutegravir plus Rilpivirine (n = 513)	Current Antiretroviral Regimen (n = 511)
Gastrointestinal		
Diarrhoea	2%	<1%
Abdominal distention	1%	0
Nausea	1%	0
Flatulence	1%	0
Nervous System		
Headache	2%	0
Dizziness	1%	<1%
Psychiatric disorders		
Insomnia	1%	<1%
Abnormal dreams	1%	0

In the pooled analyses, the proportion of subjects who discontinued treatment due to an adverse event was 4% in subjects receiving dolutegravir plus rilpivirine once daily and less than 1% in subjects who remained on their current antiretroviral regimen. The most common adverse events leading to discontinuation were psychiatric disorders: 2% of subjects receiving dolutegravir plus rilpivirine and less than 1% on the current antiretroviral regimen. The incidence of Serious Adverse Events was 5% in subjects receiving dolutegravir plus rilpivirine and 4% in subjects who remained on their current antiretroviral regimen.

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 (Table 5) 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.

Table 5: Adverse Reactions with the Individual Components of DTG/RPV FDC

System	Frequency*	DTG	RPV
Immune system disorders	Uncommon	Hypersensitivity (*see Section 4.4 SPECIAL 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

System	Frequency*	DTG	RPV
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.

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 increase

The following events have been reported with dolutegravir-containing regimens. The contribution of dolutegravir in these cases is unclear.

Blood and lymphatic systems disorders:
Very rare: sideroblastic anaemia. Reversible sideroblastic anaemia has been reported in a dolutegravir containing regimen. The contribution of dolutegravir in these cases is unclear.

Hepatobiliary disorders:
Rare: acute hepatic failure

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Pharmacodynamic effects

Antiviral activity in cell culture
Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 in peripheral blood mononuclear cells (PBMCs) and MT4 cells with mean EC_{50}s of 0.5 nM to 2.1 nM.

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
The antiviral activity of dolutegravir *in vitro* was not antagonistic with the integrase inhibitor (INI) raltegravir; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir or stavudine; the protease inhibitors (PIs) amprenavir or lopinavir; the CCR5 co-receptor antagonist maraviroc; or the fusion inhibitor enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor adefovir, or inhibited by the antiviral ribavirin.

Rilpivirine showed no antagonistic antiviral activity in combination with the NRTIs: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine; the PIs: amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs: efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide; the entry inhibitor maraviroc, and the INI raltegravir.

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
The protein adjusted EC_{90} (PA-IC_{90}) in PBMCs for dolutegravir 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
Dolutegravir-resistant viruses were selected in studies of potential resistance using different wild type strains and clades of HIV-1. Amino acid substitutions that emerged during passaging included E92Q, G193E, G118R, S153F or Y, and R263K, and were associated with decreased susceptibility to dolutegravir of up to 11-fold.

In resistance development studies starting with the single raltegravir resistance mutants Q148H, Q148K or Q148R, additional mutations detected during passage with dolutegravir included E138K/Q148K, E138K/Q148R, Q140S/Q148R and G140S/Q148R, which all exhibited greater than ten-fold reductions in sensitivity to dolutegravir.

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 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. 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 post baseline 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-naïve studies (SPRING-1, SPRING-2, SINGLE and FLAMINGO 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). A G118R substitution conferred a 10 fold reduction in dolutegravir susceptibility but has not been observed during dolutegravir clinical studies. 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. Dolutegravir had a ≤ 10 FC against 67 (73%) of the 92 clinical isolates with Q148 + ≥ 2 INSTI-resistance substitutions and 168 (91%) of the 184 isolates with Q148 + 1 INSTI resistance substitutions.

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, with 13 measurements over 24 hours at steady-state. 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

In a DEXA substudy which evaluated 81 patients, mean bone mineral density (BMD) significantly increased from baseline to week 48 in subjects who switched to dolutegravir plus rilpivirine (46 patients; 1.34% total hip and 1.46% lumbar spine) compared with those who continued on treatment with a TDF-containing antiretroviral regimen (35 patients; 0.05% total hip and 0.15% lumbar spine; p = 0.014 and p = 0.039, respectively). The effect on fracture rate was not studied. The long-term clinical significance of these BMD changes is not known.

Adrenal function

In the pooled phase III trials for rilpivirine, at Week 96, the overall mean change from baseline in basal cortisol was -19.1 nmol/L in the rilpivirine group, and -0.6 nmol/L in the efavirenz group. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine group (+18.4 ± 8.36 nmol/L) than in the efavirenz group (+54.1 ± 7.24 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 96 were within the normal range (>248nmol/L for basal and >500 nmol/L for stimulated values respectively). Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.

Clinical trials

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, multicentre, parallel-group, non-inferiority studies. Subjects were enrolled if they had been stably suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months prior to screening with no history of virological failure and had no known or suspected resistance to either dolutegravir or rilpivirine. A total of 1,024 adult HIV-1 infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 NRTIs plus either an INSTI, 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 mm^3; 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 6).

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 6.

Table 6: 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%)
Non-White	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 = dolutegravir; INSTI = Integrase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease Inhibitor; RPV = rilpivirine

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.

Children

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

5.2 PHARMACOKINETIC PROPERTIES

One JULUCA tablet is bioequivalent to one dolutegravir 50 mg tablet and one rilpivirine 25 mg tablet 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_T from 30 to 65% across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects and CVb% was estimated to be 30-50% for AUC and C_{max}, and at 55-140% for C_T. 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 16.2 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; 16.8 mg/mL at week 2 and 23 ng/mL at week 16, ranging from 3.81 to 32.1 ng/mL). CSF: plasma concentration ratio of dolutegravir ranged from 0.11 to 2.04%. Dolutegravir concentrations in CSF exceeded the IC_{50}, (0.52 nM = 0.2 ng/mL) 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 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 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.

Excretion
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 ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of total dose) were detected in urine.

Special patient populations

Paediatric population
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 mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease, increased monitoring for adverse effects is recommended.

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. Dolutegravir has not been studied 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. In patients with severe renal impairment or end stage renal disease, the combination of rilpivirine with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. 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 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.

Gender
The dolutegravir exposure in healthy subjects appears to be slightly higher (~20%) in women than men based on data obtained in a healthy subject study (males n=17, females n=24). Population pharmacokinetic analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

Rilpivirine has tested negative in the *in vitro* Ames reverse mutation assay 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.

Carcinogenicity
No carcinogenicity studies have been conducted with the combination of dolutegravir/rilpivirine

In long-term oral carcinogenicity studies conducted with dolutegravir no drug-related increases in tumour incidence were found in mice at doses up to 500 mg/kg/day (20 times the human systemic exposure based on AUC at the maximum recommended dose of 50 mg QD) or in rats at doses up to 50 mg/kg/day (17 times the human systemic exposure based on AUC at the maximum recommended dose).

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).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol
Magnesium stearate
Microcrystalline cellulose
Povidone
Sodium starch glycollate Type A,
Sodium stearylfumarate
Lactose monohydrate,
Croscarmellose sodium
Polysorbate 20
Silicified microcrystalline cellulose
Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Purified talc
Iron oxide yellow
Iron oxide red.

6.2 INCOMPATIBILITIES

No incompatibilities have been identified.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. 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

JULUCA tablets are supplied in white HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures. Each bottle contains 30 film-coated tablets and a desiccant.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Dolutegravir:
The chemical (IUPAC) name for dolutegravir sodium is Sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate.

Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$

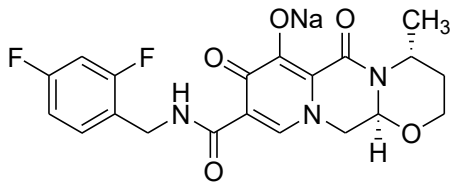
Molecular weight of 441.36 g/mol.

Rilpivirine:
The chemical name of rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride.

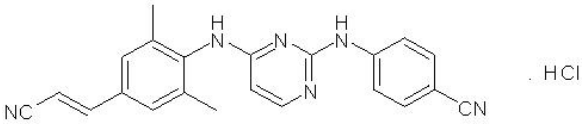
Molecular formula: $C_{22}H_{18}N_6.HCl$

Molecular weight of 402.88 g/mol.

Chemical structure
The structural formula of dolutegravir sodium is:



The structural formula of rilpivirine hydrochloride is:



CAS number
1051375-19-9 (dolutegravir sodium); 700361-47-3 (rilpivirine hydrochloride).

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

ViiV Healthcare Pty Ltd

Level 4, 436 Johnston Street

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

20 June 2018

10 DATE OF REVISION

05 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Inclusion of serum lipids and blood glucose level increase

Version 9.0