PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**JULUCA**

dolutegravir and rilpivirine tablets

50 mg dolutegravir (as dolutegravir sodium) and 25 mg rilpivirine (as rilpivirine hydrochloride)

Antiretroviral Agent

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RECENT MAJOR LABEL CHANGES

Warnings and Precautions, Hepatotoxicity (6)	08/2018
Warnings and Precautions, Pregnant Women (6.1.1)	08/2018

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JULUCA (dolutegravir/rilpivirine) is indicated as a complete regimen to replace the current antiretroviral regimen for:

- the treatment of human immunodeficiency virus (HIV-1) infection in adults who are virologically stable and suppressed (HIV-1 RNA less than 50 copies per mL).

1.1 Pediatrics

Pediatrics (< 18 years of age): Safety and efficacy of JULUCA have not been established in pediatric patients less than 18 years of age.

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of JULUCA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from adult patients < 65 years of age.

2 CONTRAINDICATIONS

JULUCA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

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

- Dofetilide, an antiarrhythmic agent
- Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; anticonvulsants
- rifampin, rifapentine; antimycobacterials
- proton pump inhibitors omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole
- systemic dexamethasone (more than a single-dose); glucocorticoid
- St John's wort (*Hypericum perforatum*) (see **Drug-Herb Interactions**)

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- As with all antiretroviral drugs, therapy should be initiated by a healthcare professional experienced in the management of HIV infection.

- JULUCA should not be used in patients with known or suspected resistance to dolutegravir or rilpivirine.

- Prior to initiating JULUCA, patients should be on stable antiretroviral therapy for at least 6 months.

3.2 Recommended Dose and Dosage Adjustment

Adults

The recommended dose of JULUCA in adults is one tablet once daily taken orally with a meal to obtain optimal absorption of rilpivirine (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pediatrics (< 18 years of age): Safety and efficacy of JULUCA have not been established in pediatric patients less than 18 years of age.

Geriatrics (> 65 years of age): Clinical studies of JULUCA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from adult patients < 65 years of age.

Rifabutin Coadministration
If JULUCA is coadministered with rifabutin, take an additional 25 mg tablet of EDURANT (rilpivirine) with JULUCA once daily with a meal for the duration of the rifabutin coadministration (see **DRUG INTERACTIONS**, Table 4 Established or Potential Drug-Drug Interactions**)**

Renal insufficiency
No dosage adjustment of JULUCA is required in patients with renal insufficiency (see **Pharmacokinetics**, Special Populations and Conditions, *Renal Insufficiency*).

Hepatic insufficiency
No dosage adjustment of JULUCA is required in patients with mild or moderate hepatic insufficiency (Child-Pugh score A or B). JULUCA has not been studied in patients with severe hepatic insufficiency (Child-Pugh score C) (see **Pharmacokinetics**, Special Populations and Conditions, *Hepatic Insufficiency*).

3.3 Missed Dose

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.

4 OVERDOSAGE

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

Treatment
There is no known specific treatment for overdose with JULUCA. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required, including monitoring of vital signs, ECG (QT interval), and observation of the clinical status of the patient. Administration of activated charcoal may be used to aid in removal of unabsorbed active substance. As dolutegravir and rilpivirine are highly bound to plasma proteins, it is unlikely they will be significantly removed by dialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
oral	tablet/ 50 mg dolutegravir (as dolutegravir sodium), 25 mg rilpivirine (as rilpivirine hydrochloride)	croscarmellose sodium, D-mannitol, iron oxide red, iron oxide yellow, lactose monohydrate, macrogol/PEG, magnesium stearate, microcrystalline cellulose, polysorbate 20, polyvinyl alcohol-part hydrolyzed, povidone K29/32 and K30, silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, talc, titanium dioxide

Each film coated tablet of JULUCA contains 50 mg dolutegravir (as 52.6 mg of dolutegravir sodium) and 25 mg rilpivirine (as 27.5 mg rilpivirine hydrochloride).

Dosage Forms
JULUCA tablets are pink, film-coated, oval, biconvex tablets debossed with ‘SV J3T’ on one side.

Packaging
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 silica gel desiccant.

6 WARNINGS AND PRECAUTIONS

General
As with other antiretroviral medicinal products, resistance testing and/or historical resistance data should guide the use of JULUCA. JULUCA should not be used in patients with known or suspected resistance to dolutegravir or rilpivirine. The SWORD studies excluded patients who had not been on stable antiretroviral therapy for at least 6 months.

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.

Patients should be advised that current antiretroviral therapy, including JULUCA, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions to prevent the transmission of HIV should continue to be taken.

Depressive Disorders
Depressive disorders (including depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, and suicidal ideation) have been reported with other rilpivirine-containing products (see **ADVERSE REACTIONS**). 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.

Hepatotoxicity
Hepatic adverse events have been reported in patients receiving other rilpivirine or other dolutegravir-containing regimens. 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 with use of rilpivirine or dolutegravir. A few cases of hepatic toxicity have been reported in adult patients receiving other rilpivirine or other dolutegravir-containing regimens who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ (dolutegravir/abacavir/lamivudine). Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with JULUCA is recommended.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions
The concomitant use of JULUCA and other drugs may result in known or potentially significant drug interactions, some of which may lead to (see **CONTRAINDICATIONS**, **DRUG INTERACTIONS**):

- Loss of therapeutic effect of JULUCA and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

In healthy subjects, 75 mg once daily rilpivirine (3 times the dose in JULUCA) and 300 mg once daily (12 times the dose in JULUCA) have been shown to prolong the QTc interval of the electrocardiogram (see **CONTRAINDICATIONS**, **DRUG INTERACTIONS**, **ACTION AND CLINICAL PHARMACOLOGY**). Consider alternatives to JULUCA when coadministered with a drug with a known risk of Torsade de Pointes. See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with JULUCA; review concomitant medications during therapy with JULUCA; and monitor for the adverse reactions associated with the concomitant drugs.

Skin and 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.

Severe skin and hypersensitivity reactions have been reported during postmarketing experience with other rilpivirine-containing regimens, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the Phase 3 clinical trials of rilpivirine, treatment-related rashes with at least Grade 2 severity were reported in 3% of patients. No Grade 4 rash was reported. Overall, most rashes were Grade 1 or 2 and occurred in the first 4 to 6 weeks of therapy (see **ADVERSE REACTIONS**).

During the Phase 3 clinical trials with dolutegravir plus rilpivirine, treatment-related rashes were reported in approximately 1% of patients, and all were Grade 1 or 2.

Discontinue JULUCA and other suspect agents immediately if signs or symptoms of severe skin or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, mucosal involvement [oral blisters or lesions], conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including laboratory parameters with 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 (see **CONTRAINDICATIONS**).

Sexual Health

Reproduction

Antiretroviral Pregnancy Registry (APR): To monitor maternal-fetal outcomes of pregnant women with HIV exposed to JULUCA and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients:
http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

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 TOXICOLOGY**).

6.1 Special Populations

6.1.1 Pregnant Women

JULUCA has not been studied in pregnant women. JULUCA should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus (see **NON-**

CLINICAL TOXICOLOGY). Women of childbearing potential (WOCBP) should undergo pregnancy testing before starting JULUCA and JULUCA should not be used in the first trimester. WOCBP who are taking JULUCA should use effective contraception throughout treatment.

In a preliminary analysis of an ongoing birth outcome surveillance study in Botswana there have been 4 cases (as of May 2018) of neural tube defects reported in 426 infants born to mothers who were exposed to dolutegravir-containing regimens from the time of conception. In the same study, no infant born to a woman who started dolutegravir during pregnancy had a neural tube defect, out of 2,824 women. 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 neural tube defects occur within the first 4 weeks of fetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Although there is limited experience with the use of dolutegravir in pregnancy, the available data from other sources including the Antiretroviral Pregnancy Registry (including over 120 completed pregnancies as of May 2018 in mothers exposed to dolutegravir at the time of conception), clinical trials and post-marketing use has not indicated a similar potential safety issue.

In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta, and no evidence of teratogenicity, reproductive function, relevant embryonic or fetal toxicity, including neural tube defects, was identified. Studies in rats and rabbits with rilpivirine have shown no evidence of relevant embryonic or fetal toxicity, effect on reproductive function, or teratogenicity (see **NON-CLINICAL TOXICOLOGY**).

6.1.2 Breast-feeding

HIV-1-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. It is expected that dolutegravir will be present in human milk based on animal data. It is not known if rilpivirine is present in human milk. HIV-1-infected mothers should be instructed not to breast-feed if they are receiving JULUCA.

6.1.3 Pediatrics

Pediatrics (<18 years): Safety and efficacy of JULUCA have not been established in pediatric patients less than 18 years of age.

6.1.4 Geriatrics

Geriatrics (>65 years): Clinical studies of JULUCA did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from adult patients less than 65 years of age.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The safety assessment of JULUCA in HIV-1-infected, virologically suppressed patients 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, multicenter, open-label studies: SWORD-1 and SWORD-2. For details on adverse reactions that have occurred in studies with EDURANT or TIVICAY, please refer to the respective product monographs.

A total of 1,024 adult HIV-1-infected patients who were on a stable suppressive antiretroviral regimen (containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI) were randomized and received treatment. Patients were randomized 1:1 to continue their current antiretroviral regimen or be switched to dolutegravir plus rilpivirine administered once daily. The rates of adverse events leading to discontinuation in the pooled analysis were 4% in patients receiving dolutegravir plus rilpivirine once daily and less than 1% in patients who remained on their current antiretroviral regimen. The most common adverse events leading to discontinuation were psychiatric disorders; 2% of patients receiving dolutegravir plus rilpivirine and less than 1% on the current antiretroviral regimen.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 2% of patients in either treatment arm of the pooled analysis of the SWORD-1 and SWORD-2 trials are provided in Table 2. The ADRs observed for dolutegravir plus rilpivirine in the Week 48 analysis of the pooled data from Phase 3 clinical trials were consistent with the ADR profiles and severities for the individual components when administered with other antiretroviral agents. No additional ADRs or increased frequency or severity of ADRs were observed with the combination of dolutegravir plus rilpivirine.

Table 2 Treatment-Emergent Adverse Drug Reactions (Grades 1 to 4) and at Least 2% Frequency in Virologically Suppressed Patients (Week 48 Pooled Analyses)

SOC	SWORD 1 DTG plus RPV (n = 252) n (%)	SWORD 1 CAR (n=256) n (%)	SWORD 2 DTG plus RPV (n = 261) n (%)	SWORD 2 CAR (n=255) n (%)	POOLED DTG plus RPV (n = 513) n (%)	POOLED CAR (n = 511) n (%)
Gastrointestinal						
Diarrhea	4 (2%)	1 (<1%)	4 (2%)	0	8 (2%)	1 (<1%)
Abdominal Distension	5 (2%)	0	2 (<1%)	0	7 (1%)	0
Nausea	4 (2%)	0	3 (1%)	0	7 (1%)	0
Flatulence	1 (<1%)	0	5 (2%)	0	6 (1%)	0
General Disorders						
Fatigue	5 (2%)	0	0 (0%)	0	5 (<1%)	0
Nervous System						
Headache	5 (2%)	0	6 (2%)	0	11 (2%)	0
Dizziness	2 (<1%)	1 (<1%)	4 (2%)	0	6 (1%)	1 (<1%)

SOC = System Organ Class/Preferred Term, CAR = current antiretroviral therapy, DTG = dolutegravir, RPV = rilpivirine

7.3 Less Common Clinical Trial Adverse Reactions

The following ADRs occurred in less than 2% of patients receiving dolutegravir plus rilpivirine or are from studies described in the product monographs of the individual components TIVICAY (dolutegravir) and EDURANT (rilpivirine). Some events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, nausea, upper abdominal pain, vomiting.

General Disorders: Fatigue.

Hepatobiliary Disorders: Cholecystitis, cholelithiasis, hepatitis.

Immune System Disorders: Hypersensitivity, Immune reconstitution inflammatory syndrome.

Metabolism and Nutrition Disorders: Decreased appetite.

Musculoskeletal Disorders: Myalgia, Myositis.

Nervous System Disorders: Dizziness, somnolence.

Psychiatric Disorders: Anxiety, depressed mood, depression, insomnia, abnormal dreams, sleep disorders, suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness).

Renal and Urinary Disorders: Glomerulonephritis membranous, glomerulonephritis, mesangioproliferative, nephrolithiasis, renal insufficiency.

Skin and Subcutaneous Tissue Disorders: Pruritus, rash.

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity experienced in at least 2% of patients are presented in Table 3.

Table 3 Selected Laboratory Abnormalities (Grades 2 and 3 to 4; Week 48 Pooled Analyses)

Laboratory Parameter Preferred Term	Dolutegravir plus Rilpivirine (n = 513) n (%)	Current Antiretroviral Regimen (n = 511) n (%)
ALT		
Grade 2 (>2.5-5.0 x ULN)	8 (2%)	4 (<1%)
Grade 3 to 4 (>5.0 x ULN)	3 (<1%)	3 (<1%)
AST		
Grade 2 (>2.5-5.0 x ULN)	5 (<1%)	8 (2%)
Grade 3 to 4 (>5.0 x ULN)	3 (<1%)	4 (<1%)
Total Bilirubin		
Grade 2 (1.6-2.5 x ULN)	11 (2%)	18 (4%)
Grade 3 to 4 (>2.5 x ULN)	0	13 (3%)
Creatine kinase		
Grade 2 (6.0-9.9 x ULN)	4 (<1%)	5 (<1%)
Grade 3 to 4 (≥10.0 x ULN)	6 (1%)	11 (2%)
Hyperglycemia		
Grade 2 (126-250 mg/dL)	21 (4%)	26 (5%)
Grade 3 to 4 (>250 mg/dL)	5 (<1%)	1 (<1%)
Hypophosphataemia		
Grade 2 (0.45 <0.65 mmol/L)	44 (9%)	79 (15%)
Grade 3 to 4 (<0.32 mmol/L)	3 (<1%)	11 (2%)
Lipase		
Grade 2 (>1.5-3.0 x ULN)	25 (5%)	24 (5%)
Grade 3 to 4 (>3.0 x ULN)	11 (2%)	11 (2%)

ULN = Upper limit of normal.

Serum Lipids: No clinically relevant changes in lipid profiles were noted throughout the 48 weeks in either treatment arm.

Changes in Serum Creatinine: 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).

Co-infection with Hepatitis B or C: A higher incidence of Grade 1 liver chemistry elevations was observed in patients treated with dolutegravir plus rilpivirine co-infected with hepatitis C compared with those who were not co-infected. JULUCA has not been studied in patients with hepatitis B co-infection.

Bone Mineral Density Effects

Mean bone mineral density (BMD) increased from baseline to Week 48 in subjects who switched from an antiretroviral treatment (ART) regimen containing tenofovir disoproxil fumarate (TDF) 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 dual-energy X-ray absorptiometry (DXA) substudy. BMD declines of 5% or greater at the lumbar spine were experienced by 2% of subjects receiving JULUCA and 5% of subjects who continued their TDF-containing regimen. The long-term clinical significance of these BMD changes is not known.

Fractures (excluding fingers and toes) were reported in 3 (0.6%) subjects who switched to dolutegravir plus rilpivirine and 9 (1.8%) subjects who continued their current antiretroviral regimen through 48 weeks.

Adrenal Function

In the pooled Phase 3 trials results analysis of rilpivirine, at Week 96, there was an overall mean change from baseline in basal cortisol of -0.69 (-1.12, 0.27) micrograms/dL in the rilpivirine group and of -0.02 (-0.48, 0.44) micrograms/dL in the efavirenz group. The clinical significance of the higher abnormal rate of 250 micrograms ACTH stimulation tests in the rilpivirine group is not known. Refer to the EDURANT (rilpivirine) Prescribing Information for additional information.

7.5 Clinical Trial Adverse Reactions (Pediatrics)

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

7.6 Post-Market Adverse Reactions

These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to dolutegravir- or rilpivirine-containing regimens, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Hepatobiliary Disorders: Acute liver failure, hepatotoxicity

Musculoskeletal and connective disorders: arthralgia, myalgia

Renal and Genitourinary Disorders: Nephrotic syndrome

Skin and Subcutaneous Tissue Disorders: Severe skin and hypersensitivity reactions including DRESS (see **WARNINGS AND PRECAUTIONS**).

Investigations: weight increased

8 DRUG INTERACTIONS

8.1 Overview

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. Because JULUCA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided. For more information on these interactions, please refer to the EDURANT and TIVICAY product monographs.

8.2 Drug-Drug Interactions

In vitro, dolutegravir inhibited the renal organic cation transporters, (OCT)2 (IC_{50} = 1.93 µM), multidrug and toxin extrusion transporter (MATE)-1 (IC_{50} = 6.34 micromolar) and MATE2-K (IC_{50} = 24.8 micromolar). *In vivo,* dolutegravir has a low potential to affect the transport of MATE2-K substrates. *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2. Dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 (dofetilide [see **CONTRAINDICATIONS**], metformin) or MATE1 (see Table 4).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC_{50} = 2.12 micromolar) and OAT3 (IC_{50} = 1.97 micromolar). Based upon the dolutegravir unbound plasma concentration, in silico modelling and lack of notable effect on the *in vivo* pharmacokinetics of the OAT substrates tenofovir and para aminohippurate, dolutegravir has a low propensity to cause drug interactions via inhibition of OAT transporters.

Effect of Other Agents on the Pharmacokinetics of Dolutegravir or Rilpivirine

Dolutegravir
Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP *in vitro*; therefore drugs that induce those enzymes and transporters, may decrease dolutegravir plasma concentrations 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 concentrations (see Table 4).

In vitro, dolutegravir is not a substrate of human OATP1B1, OATP1B3, or OCT1.

Coadministration of dolutegravir with polyvalent cation-containing products may lead to decreased absorption of dolutegravir.

Rilpivirine

Rilpivirine is primarily metabolized 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.

Coadministration of JULUCA with drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs.

QT-Prolonging Drugs: In healthy subjects, 75 mg once daily rilpivirine (3 times the dose in JULUCA) and 300 mg once daily (12 times the dose in JULUCA) have been shown to prolong the QTc interval of the electrocardiogram (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Effects on Electrocardiogram). Consider alternatives to JULUCA when coadministered with a drug with a known risk of Torsade de Pointes.

Established or Potential Drug Interactions

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table 4. The drugs listed in this table are not all-inclusive. Recommendations are based on either drug interaction studies, or potential or predicted interactions due to the expected magnitude of interaction and/or potential for serious adverse events or loss of efficacy.

Table 4 Established or Potential Drug-Drug Interactions

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug***	**Clinical comment**
Dofetilide	Effect of dolutegravir: Dofetilide ↑	Co-administration of JULUCA with dofetilide is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentrations.
Anticonvulsants: Carbamazepine, Oxcarbazepine, Phenytoin, Phenobarbital	Effect of carbamazepine: Dolutegravir ↓ Rilpivirine ↓	Co-administration is contraindicated.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug*	Clinical comment
Proton Pump Inhibitors: Omeprazole† Lansoprazole Rabeprazole Pantoprazole Esomeprazole	Dolutegravir ↔ Rilpivirine ↓ (by omeprazole) Omeprazole ↓ (by rilpivirine)	Co-administration is contraindicated.
H_2-Receptor Antagonists: Famotidine† Cimetidine Nizatidine Ranitidine	Dolutegravir ↔ Famotidine taken 12 hrs before Rilpivirine: Rilpivirine↔ Famotidine taken 2 hrs before Rilpivirine: Rilpivirine ↓ Famotidine taken 4 hrs after Rilpivirine: Rilpivirine ↔	JULUCA should be administered at least 4 hours before or at least 12 hours after H_2-receptor antagonists.
Antacids (e.g. aluminium or, magnesium hydroxide, and/or calcium carbonate:	Dolutegravir ↓ Rilpivirine ↓	JULUCA should be administered at least 4 hours before or 6 hours after taking antacids.
Medications containing polyvalent cations (e.g. Mg or Al): Cation-containing products[b] or laxatives Sucralfate Buffered medications	Dolutegravir ↓	JULUCA should be administered at least 4 hours before or 6 hours after taking products containing polyvalent cations.
Calcium and Iron supplements, including multivitamins containing calcium or iron[b] (Non-antacid)	Calcium: Dolutegravir ↓ Iron: Dolutegravir ↓	JULUCA is recommended to be administered at least 4 hours before or 6 hours after taking calcium or iron supplements (non-antacids) Alternatively, JULUCA and supplements containing calcium or iron can be taken together with a meal.
Antidiabetics: Metformin[b]	Co-administered with dolutegravir: Metformin ↑ Co-administered with rilpivirine: Metformin ↔	Consider metformin dose adjustments when starting or stopping concomitant treatment to maintain glycemic control.
Rifampin† Rifapentine	Dolutegravir ↓ Rifampin ↔ Rilpivirine ↓	Co-administration is contraindicated.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug*	Clinical comment
Antimycobacterials: Rifabutin[b]	Dolutegravir ↔ Rifabutin ↔ Rilpivirine ↓	Rifabutin decreased the plasma concentrations of rilpivirine. An additional rilpivirine 25 mg tablet should be taken with JULUCA once daily with a meal when rifabutin is co-administered.
Dexamethasone (systemic, except for single dose use)	Rilpivirine ↓ Dolutegravir ↔	Co-administration is contraindicated, except for single dose use.
Narcotic analgesics: Methadone[b]	Effect of dolutegravir: Methadone ↔ Effect of rilpivirine: R(-), S(+) Methadone ↓	No dose adjustment is necessary. 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 ↑ Ketoconazole ↓	No dose adjustment is necessary.
Macrolide or ketolide antibiotics: Clarithromycin Erythromycin Telithromycin	Dolutegravir ↔ Rilpivirine ↑	No dose adjustment is necessary.

Legend; ↑ = Increase; ↓ =decrease; ↔ = no significant change

† 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.

[b] See Tables 5 to 8 for magnitude of interaction.

The effects of DTG and RPV on the exposure of co-administered drugs are shown in Table 5 and Table 7, respectively. The effects of co-administered drugs on the exposure of DTG and RPV are shown in Table 6 and Table 8, respectively.

Table 5 Summary of Effect of Dolutegravir on the Pharmacokinetics of Co-administered Drugs

Co-administered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Co-administered Drug With/Without Dolutegravir No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.06 (0.88 to 1.29)	0.98 (0.83 to 1.15)	1.03 (0.84 to 1.25)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	1.02 (0.93, 1.11)	1.03 (0.96, 1.11)	0.99 (0.91, 1.08)
Methadone 16 to 150 mg	50 mg twice daily	12	0.99 (0.91, 1.07)	0.98 (0.91, 1.06)	1.00 (0.94, 1.06)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79, 1.15)	_
Norgestimate 0.25 mg	50 mg twice daily	15	0.93 (0.85, 1.03)	0.98 (0.91, 1.04)	0.89 (0.82, 0.97)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.21 (1.07, 1.38)	1.06 (0.98, 1.16)	1.10 (0.99, 1.22)
Metformin 500 mg twice daily	50 mg once daily	14	_	1.79 (1.65, 1.93)	1.66 (1.53, 1.81)
Metformin 500 mg twice daily	50 mg twice daily	14	_	2.45 (2.25, 2.66)	2.11 (1.91, 2.33)

Table 6 Summary of Effect of Co-administered Drugs on the Pharmacokinetics of Dolutegravir

Co-administered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters With/Without Co-administered Drugs No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Maalox®	50 mg single dose	16	0.26 (0.21, 0.31)	0.26 (0.22, 0.32)	0.28 (0.23, 0.33)
Maalox® 2 hrs after dolutegravir	50 mg single dose	16	0.70 (0.58, 0.85)	0.74 (0.62, 0.90)	0.82 (0.69, 0.98)
Calcium Carbonate 1200 mg simultaneous administration (fasted)	50 mg single dose	12	0.61 (0.47, 0.80)	0.61 (0.47, 0.80)	0.63 (0.50, 0.81)
Calcium Carbonate 1200 mg simultaneous administration (fed)	50 mg single dose	11	1.08 (0.81, 1.42)	1.09 (0.84, 1.43)	1.07 (0.83, 1.38)
Calcium Carbonate 1200 mg 2 hrs after dolutegravir	50 mg single dose	11	0.90 (0.68, 1.19)	0.94 (0.72, 1.23)	1.00 (0.78, 1.29)
Ferrous Fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.44 (0.36, 0.54)	0.46 (0.38, 0.56)	0.43 (0.35, 0.52)
Ferrous Fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.00 (0.81, 1.23)	0.98 (0.81, 1.20)	1.03 (0.84, 1.26)
Ferrous Fumarate 324 mg 2 hrs after dolutegravir	50 mg single dose	10	0.92 (0.74, 1.13)	0.95 (0.77, 1.15)	0.99 (0.81, 1.21)
Multivitamin One tablet once daily	50 mg single dose	16	0.68 (0.56, 0.82)	0.67 (0.55 , 0.81)	0.65 (0.54, 0.77)
Omeprazole 40 mg once daily	50 mg single dose	12	0.95 (0.75, 1.21)	0.97 (0.78, 1.20)	0.92 (0.75, 1.11)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.17 (1.06, 1.28)	1.11 (1.03, 1.20)	1.06 (0.99, 1.14)
Rifampin[a] 600 mg once daily	50 mg twice daily[a]	11	0.28 (0.23, 0.34)	0.46 (0.38, 0.55)	0.57 (0.49, 0.65)
Rifampin[b] 600 mg once daily	50 mg twice daily[b]	11	1.22 (1.01, 1.48)	1.33 (1.15, 1.53)	1.18 (1.03, 1.37)

Co-administered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters With/Without Co-administered Drugs No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Rifabutin 300 mg once daily	50 mg once daily	9	0.70 (0.57, 0.87)	0.95 (0.82, 1.10)	1.16 (0.98, 1.37)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.22 (1.15, 1.30)	1.12 (1.05, 1.19)	1.13 (1.06, 1.21)
Telaprevir 750 mg every 8 hours	50 mg once daily	15	1.37 (1.29, 1.45)	1.25 (1.20, 1.31)	1.18 (1.11, 1.26)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.08 (0.91, 1.28)	1.07 (0.95, 1.20)	1.05 (0.96, 1.15)
Carbamazepine 300 mg twice daily	50 mg once daily	14	0.27 (0.24, 0.31)	0.51 (0.48, 0.55)	0.67 (0.61, 0.73)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.45 (1.25 to 1.68)	1.33 (1.11 to 1.59)	1.29 (1.07 to 1.57)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

Table 7 Summary of Effect of Rilpivirine on the Pharmacokinetics of Co-administered Drugs

Co-administered Drug(s) and Dose(s)	Dose of Rilpivirine	n	Geometric Mean Ratio (90% CI) of Co-administered Drug Pharmacokinetic Parameters with/without EDURANT No Effect = 1.00		
			C_{min}	AUC	C_{max}
Co-administration with other Antivirals					
Simeprevir 150 mg once daily	25 mg once daily	21	0.96 (0.83, 1.11)	1.06 (0.94, 1.19)	1.10 (0.97, 1.26)
Telaprevir 25 mg once daily	750 mg every 8 hours	13	0.89 (0.67, 1.18)	0.95 (0.76, 1.18)	0.97 (0.76, 1.21)
Co-administration with other Drugs					
Acetaminophen 500 mg single dose	150 mg once daily[a]	16	NA	0.91 (0.86, 0.97)	0.97 (0.86, 1.10)
Atorvastatin 40 mg once daily	150 mg once daily[a]	16	0.85 (0.69, 1.03)	1.04 (0.97, 1.12)	1.35 (1.08, 1.68)
Chlorzoxazone 500 mg single dose taken 2 hours after rilpivirine	150 mg once daily[a]	16	NA	1.03 (0.95, 1.13)	0.98 (0.85, 1.13)
Digoxin 0.5 mg single dose	25 mg once daily	22	NA	0.98 (0.93, 1.04)[c]	1.06 (0.97, 1.17)
Ethinylestradiol 0.035 mg once daily Norethindrone 1 mg once daily	25 mg once daily	17	1.09 (1.03, 1.16) 0.99 (0.90, 1.08)	1.14 (1.10, 1.19) 0.89 (0.84, 0.94)	1.17 (1.06, 1.30) 0.94 (0.83, 1.06)
Ketoconazole 400 mg once daily	150 mg once daily[a]	14	0.34 (0.25, 0.46)	0.76 (0.70, 0.82)	0.85 (0.80, 0.90)
Methadone 60-100 mg once daily, individualized dose R(-) methadone S(+) methadone	25 mg once daily	13	 0.78 (0.67, 0.91) 0.79 (0.67, 0.92)	 0.84 (0.74, 0.95) 0.84 (0.74, 0.96)	 0.86 (0.78, 0.95) 0.87 (0.78, 0.97)
Metformin 850 mg single dose	25 mg once daily	20	NA	0.97 (0.90, 1.06)[b]	1.02 (0.95, 1.10)
Omeprazole 20 mg once daily	150 mg once daily[a]	15	NA	0.86 (0.76, 0.97)	0.86 (0.68, 1.09)
Rifabutin 300 mg once daily	150 mg Once daily [a]	17	1.01 (0.94, 1.09)	1.03 (0.97,1.09)	1.03 (0.93,1.14)
Rifampin 600 mg once daily	150 mg once daily[a]	16	NA	0.99 (0.92, 1.07)	1.02 (0.93, 1.12)
Sildenafil 50 mg single dose	75 mg once daily[a]	16	NA	0.97 (0.87, 1.08)	0.93 (0.80, 1.08)

CI = Confidence Interval; n = Maximum number of patients with data; NA = Not available.
[a] This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the co-administered drug.
[b] N (maximum number of patients with data) for $AUC_{(0-\infty)}$ = 15.
[c] $AUC_{(0\text{-last})}$.

Table 8 Summary of Effect of Co-administered Drugs on the Pharmacokinetics of Rilpivirine

Co-administered Drug(s) and Dose(s)	Dose of Rilpivirine	n	Geometric Mean Ratio (90% CI) of Rilpivirine Pharmacokinetic Parameters with/without Co-administered Drugs No Effect = 1.00		
			C_{min}	AUC	C_{max}
Other Antivirals					
Simeprevir 150 mg once daily	25 mg once daily	23	1.25 (1.16, 1.35)	1.12 (1.05, 1.19)	1.04 (0.95, 1.13)
Other Drugs					
Acetaminophen 500 mg single dose	150 mg once daily[a]	16	1.26 (1.16, 1.38)	1.16 (1.10, 1.22)	1.09 (1.01, 1.18)
Atorvastatin 40 mg once daily	150 mg once daily[a]	16	0.90 (0.84, 0.96)	0.90 (0.81, 0.99)	0.91 (0.79, 1.06)
Chlorzoxazone 500 mg single dose taken 2 hours after rilpivirine	150 mg once daily[a]	16	1.18 (1.09, 1.28)	1.25 (1.16, 1.35)	1.17 (1.08, 1.27)
Ethinylestradiol/ Norethindrone 0.035 mg once daily/ 1 mg once daily	25 mg once daily	15	$\leftrightarrow$[b]	$\leftrightarrow$[b]	$\leftrightarrow$[b]
Famotidine 40 mg single dose taken 12 hours before rilpivirine	150 mg single dose[a]	24	N.A.	0.91 (0.78, 1.07)	0.99 (0.84, 1.16)
Famotidine 40 mg single dose taken 2 hours before rilpivirine	150 mg single dose[a]	23	N.A.	0.24 (0.20, 0.28)	0.15 (0.12, 0.19)
Famotidine 40 mg single dose taken 4 hours after rilpivirine	150 mg single dose[a]	24	N.A.	1.13 (1.01, 1.27)	1.21 (1.06, 1.39)
Ketoconazole 400 mg once daily	150 mg once daily[b]	15	1.76 (1.57, 1.97)	1.49 (1.31, 1.70)	1.30 (1.13, 1.48)
Methadone 60-100 mg once daily, individualised dose	25 mg once daily	12	$\leftrightarrow$[b]	$\leftrightarrow$[b]	$\leftrightarrow$[b]
Omeprazole 20 mg once daily	150 mg once daily[a]	16	0.67 (0.58, 0.78)	0.60 (0.51, 0.71)	0.60 (0.48, 0.73)
Rifabutin 300 mg once daily	25 mg once daily	18	0.52 (0.46, 0.59)	0.58 (0.52, 0.65)	0.69 (0.62, 0.76)

Co-administered Drug(s) and Dose(s)	Dose of Rilpivirine	n	Geometric Mean Ratio (90% CI) of Rilpivirine Pharmacokinetic Parameters with/without Co-administered Drugs No Effect = 1.00		
			C_{min}	AUC	C_{max}
Rifabutin 300 mg once daily	50 mg once daily	18	0.93 (0.85, 1.01)	1.16 (1.06, 1.26)	1.43 (1.30, 1.56)
			(as compared to 25 mg once daily rilpivirine alone)		
Rifampin 600 mg once daily	150 mg once daily[a]	16	0.11 (0.10, 0.13)	0.20 (0.18, 0.23)	0.31 (0.27, 0.36)
Sildenafil 50 mg single dose	75 mg once daily[a]	16	1.04 (0.98, 1.09)	0.98 (0.92, 1.05)	0.92 (0.85, 0.99)

CI = Confidence Interval; n = Maximum number of patients with data; N.A. = Not available; ↔ = No change.

[a] This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the co-administered drug.

[b] Comparison based on historic controls.

8.3 Drug-Food Interactions

JULUCA must be taken with a meal to ensure optimal rilpivirine plasma concentration. A protein-rich nutritional drink or meal replacement drink is not considered a meal (see **ACTION AND CLINICAL PHARMACOLOGY**). The effect of a high fat, high calorie meal on the absorption of dolutegravir and rilpivirine when administered as a fixed-dose combination tablet has not been assessed in an appropriately designed study.

8.4 Drug-Herb Interactions

Co-administration of JULUCA with products containing St. John's wort may significantly decrease dolutegravir and rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of JULUCA with products containing St. John's wort is contraindicated.

8.5 Drug-Laboratory Test Interactions

No Drug-Laboratory test interactions have been identified.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 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 IC50 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.

9.2 Pharmacodynamics

In a randomized, dose-ranging trial, HIV-1-infected patients treated with dolutegravir monotherapy demonstrated rapid and dose-dependent antiviral activity with mean declines from baseline to Day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 $\log_{10}$ for dolutegravir 2 mg, 10 mg, and 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the last dose in the 50-mg group.

Effects on Electrocardiogram

Dolutegravir
In a randomized, 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).

Rilpivirine
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. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction was 2.0 (5.0) msec (i.e., below the threshold of clinical concern).

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, randomized, 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.

9.3 Pharmacokinetics

The pharmacokinetic (PK) properties of the components of JULUCA are provided in Table 9.

Table 9 Pharmacokinetic Properties of the Components of JULUCA

	Dolutegravir	Rilpivirine
Absorption		
AUC_T [a] (ng.h/mL)	68166.3 (24.4)	3349.4 (36.5)
C_{max} [a] (ng/mL)	3703.3 (17.5)	100.1 (33.6)
T_{max} (h)[b]	3.0 (0.5 – 6.0)	4.0 (1.0 – 9.0)
Effect of moderate fat meal (relative to fasting) on AUC (%) [c]	187.5 (154.7 – 227.4)	157.1 (123.6 – 199.8)
Effect of moderate fat meal (relative to fasting) on C_{max} (%) [c]	174.9 (140.3 – 218.1)	189.1 (133.9 – 266.9)
Effect of high fat meal (relative to fasting)	Not assessed[d]	
Distribution		
% Bound to human plasma proteins	~99	~99
Source of protein binding data	in vitro	in vitro
Blood-to-plasma ratio	0.5	0.7
Metabolism		
Primarily metabolized	UGT1A1 CYP3A (minor)	CYP3A
Elimination		
Major route of elimination	Metabolism	Metabolism
$t_{1/2}$ (h)[a]	15.0 (19.2%)	59.2 (45.7)
% of dose excreted as total ^{14}C (unchanged drug) in urine[e]	31 (<1)	6.5 (<1)
% of dose excreted as total ^{14}C (unchanged drug) in feces[e]	64 (53)	85 (25)

a Arithmetic mean (CV%) after single dose administration with a moderate fat meal (see **CLINICAL TRIALS**, Comparative Bioavailability Studies). Moderate fat meal [~625 kcal: 125 kcal from protein (20%), 300 kcal from carbohydrate (48%), and 200 kcal from fat (32%)]. AUCT= AUC_{0-120} for dolutegravir and AUC_{0-264} for rilpivirine

b Median (range) after single dose administration with a moderate fat meal (see **CLINICAL TRIALS**, Comparative Bioavailability Studies).

c Geometric mean ratio (fed/fasted) (90% confidence interval). Moderate-fat meal = ~625 kcal, 32% fat.

d The effect of a high fat, high calorie meal on the absorption of dolutegravir and rilpivirine when administered as a fixed-dose combination tablet has not been assessed in an appropriately designed study.

e Dosing in mass balance studies: single-dose administration of [^{14}C] dolutegravir or [^{14}C] rilpivirine.

The JULUCA tablet taken with a moderate fat meal [approximately 625 kcal, 32% from fat] is bioequivalent to dolutegravir 50 mg and rilpivirine 25 mg tablets administered together with a meal (see **CLINICAL TRIALS**, Comparative Bioavailability Studies).

Absorption: After oral administration of JULUCA with a moderate-fat meal, dolutegravir is absorbed with a median T_{max} at 3 hours and rilpivirine is absorbed with a median T_{max} of 4 hours (see **CLINICAL TRIALS**, Comparative Bioavailability Studies).

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

Effect of Food on Oral Absorption
JULUCA should be taken with a meal. When JULUCA was taken with a meal, the absorption of both dolutegravir and rilpivirine was increased. Moderate 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 C_{max} by 89%, compared to fasted conditions.

When administered in a single dose as TIVICAY tablets, 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.

When administered in a single dose as EDURANT tablets, 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.

The effect of a high fat, high calorie meal on the absorption of dolutegravir and rilpivirine when administered as a fixed-dose combination tablet has not been assessed in an appropriately designed study.

Distribution: Dolutegravir is highly bound (≥ 98.9%) to human plasma proteins based on *in vivo* data and binding is independent of plasma dolutegravir concentration. The apparent volume of distribution (Vd/F) following 50 mg once daily oral administration was estimated at 17.4 L based on population pharmacokinetic analysis. Rilpivirine is highly bound (approximately 99.7%) to plasma proteins *in vitro*, primarily to albumin.

Cerebrospinal Fluid (CSF)
In 12 treatment-naïve patients on dolutegravir plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (ranging from 4 to 23 ng/mL) 2 to 6 hours post-dose after 2 weeks of treatment. The clinical relevance of this finding has not been established.

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. 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.

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 feces and urine, respectively. In feces, 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 Populations and Conditions

Pediatrics: JULUCA has not been studied in the pediatric population.

Geriatrics: 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 patients >65 years old are limited.

Sex: Population pharmacokinetic analyses revealed no clinically relevant effect of gender on the exposure of dolutegravir or rilpivirine.

Genetic Polymorphism: 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). Rilpivirine pharmacokinetics are not anticipated to be impacted by polymorphisms in drug metabolising enzymes.

Ethnic origin: Population pharmacokinetic analyses of both dolutegravir and rilpivirine in HIV infected patients indicated that race had no clinically relevant effect on exposure to either dolutegravir or rilpivirine.

Hepatic Insufficiency: Dolutegravir and rilpivirine are primarily metabolized and eliminated by the liver. No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score A or B). In a study comparing 8 patients with moderate hepatic insufficiency (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 insufficiency (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic insufficiency (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic insufficiency and 5% higher in patients with moderate hepatic insufficiency. The effect of severe hepatic insufficiency (Child-Pugh score C) on the pharmacokinetics of dolutegravir or rilpivirine have not been studied.

Renal Insufficiency: Population pharmacokinetic analyses indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. Dolutegravir AUC, Cmax, and C24 were lower by 40%, 23%, and 43%, respectively, in subjects (n = 8) with severe renal impairment (creatinine clearance less than 30 mL/min) as compared with matched healthy controls. Dolutegravir has not been studied in patients requiring dialysis. Population pharmacokinetic analyses indicated that mild renal impairment had no clinically relevant effect on the exposure of rilpivirine. There is limited or no information regarding the pharmacokinetics of rilpivirine in patients with moderate or severe renal impairment, end-stage renal disease, or patients requiring dialysis.

Hepatitis B or Hepatitis C Co-infection: Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir or rilpivirine. Patients with hepatitis B co-infection were excluded from studies with JULUCA.

10 STORAGE, STABILITY AND DISPOSAL

Store JULUCA up to 30ºC, and in the original package to protect from moisture. Keep the bottle tightly closed. Do not remove the silica gel desiccant.

Healthcare professionals should recommend that their patients return all unused medications to a pharmacy for proper disposal.

11 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Dolutegravir

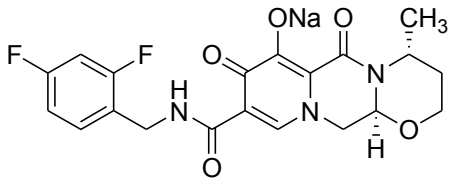
Drug Substance

Common name: dolutegravir sodium

Chemical name: sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate

Molecular formula and molecular mass: $C_{20}H_{18}F_2N_3NaO_5$
441.36 g/mol

Structural formula:



Physicochemical properties: Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Rilpivirine

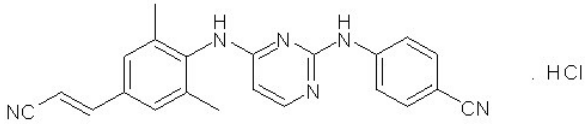
Drug Substance

Common name: rilpivirine hydrochloride

Chemical name: 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride

Molecular formula and molecular mass: $C_{22}H_{18}N_6 . HCl$
402.88 g/mol

Structural formula:



Physicochemical properties: Description: Rilpivirine hydrochloride is a white to almost white powder.
Solubility: Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

The efficacy of JULUCA is supported by data from 2 randomized, 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 patients 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. Patients were randomised 1:1 to continue their CAR or be switched to a two-drug regimen of dolutegravir plus rilpivirine administered once daily. At Week 52, patients who were originally assigned to continue their CAR and remained virologically suppressed switched to dolutegravir plus rilpivirine and are planned to be followed to Week 148. The primary efficacy endpoint for the SWORD studies was the proportion of patients virologically suppressed defined as plasma HIV-1 RNA less than 50 copies per mL at Week 48 (Snapshot algorithm for the ITT-E population).

In the pooled analysis, 54%, 26%, and 20% of patients were receiving an NNRTI, PI, or INSTI (respectively) as their baseline core agent class prior to randomization. The demographic baseline characteristics and core agent class were similarly distributed between treatment arms (see Table 10).

Table 10 Summary of Baseline Characteristics for Studies SWORD-1 (201636), SWORD-2 (201637), and Pooled Data (ITT-E Population)

	SWORD-1		SWORD-2		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	N=252 (%)	N=256 (%)	N=261 (%)	N=255 (%)	N=513 (%)	N=511 (%)
Baseline HIV-1 RNA (c/mL)						
<50 c/mL	247(98)	253 (99)	259 (99)	251 (98)	506 (99)	504 (99)
≥50 c/mL	5 (2)	3 (1)	2 (1)	4 (2)	7 (1)	7 (1)
Baseline CD4+ (log_{10} cells/mm^3)						
Median	2.786	2.805	2.785	2.798	2.786	2.805
Min., Max.	1.57, 3.18	1.98, 3.18	2.06, 3.25	2.03, 3.22	1.57, 3.25	1.98, 3.22
Age (y) median (range)	43.0 (23-78)	43.0 (22-76)	43.0 (21-79)	43.0 (22-69)	43.0 (21-79)	43.0 (22-76)
Sex						
Female	58 (23)	51(20)	62 (24)	57 (22)	120 (23)	108 (21)
Male	194 (77)	205 (80)	199 (76)	198 (78)	393 (77)	403 (79)
Race, n(%)						
American Indian or Alaska Native	3 (1)	6 (2)	11 (4)	8 (3)	14 (3)	14 (3)
Asian	25 (10)	34 (13)	13 (5)	16 (6)	38 (7)	50 (1)
Black/African American	24 (10)	27 (11)	13 (5)	20 (8)	37 (7)	47 (9)
White	198 (79)	188 (73)	223 (85)	210 (82)	421 (82)	398 (78)
Hepatitis B & C Test Results						
C only	15 (6)	19 (7)	13 (5)	21 (8)	28 (5)	40 (8)
CDC Category						
A:	203 (81)	198 (77)	197 (75)	187 (73)	400 (78)	385 (75)
B:	20 (8)	35 (14)	35 (13)	33 (13)	55 (11)	68 (13)
C:	29 (12%)	23 (9%)	29 (11%)	34 (13%)	58 (11%)	57 (11%)

13.2 Study Results

The pooled primary analysis demonstrated that dolutegravir plus rilpivirine is non-inferior to CAR, with 95% of patients in both arms achieving the primary endpoint of <50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm [ITT-E Population (Table 11)].

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 11.

Table 11 Virologic Outcomes of Randomized Treatment at Week 48 (Snapshot Algorithm, ITT-E Population)

	SWORD-1 and SWORD-2 Pooled Data	
	Dolutegravir plus Rilpivirine (N=513) n (%)	**Current Antiretroviral Regimen (N=511) n (%)**
HIV-1 RNA <50 copies/mL	(486/513) 95%	(485/511) 95%
Treatment Difference*	-0.2% (95% CI: -3.0%, 2.5%)	
Virologic non response†	3 (<1%)	6 (1%)
Reasons		
Data in window not <50 copies/mL	0	2 (<1%)
Discontinued for lack of efficacy	2 (<1%)	2 (<1%)
Discontinued for other reasons while not <50 copies/mL	1 (<1%)	1 (<1%)
Change in (ART)	0	1 (<1%)
No virologic data at Week 48 window	24 (5%)	20 (4%)
Reasons		
Discontinued study/study drug due to adverse event or death	17 (3%)	3 (<1%)
Discontinued study/study drug for other reasons**	7 (1%)	16 (3%)
Missing data during window but on study	0	1 (<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 Core 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%)

* Treatment difference [(dolutegravir plus rilpivirine)–current antiretroviral regimen] Adjusted for baseline stratification factors and assessed using a non-inferiority margin of -8% (Intent-to-Treat Exposed population).

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

**Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation

All subgroup results (i.e. CD4+ cell count, age, gender, race, and baseline core agent class) were consistent with the primary analysis.

13.3 Comparative Bioavailability Studies

A single-dose, 2-period, randomized, open-label, crossover study was conducted to evaluate the pivotal bioequivalence of an oral 1 x JULUCA (50 mg dolutegravir/25 mg rilpivirine) fixed dose combination tablet compared with co-administration of the separate tablet formulations of a 1 x TIVICAY (dolutegravir 50 mg) tablet and a 1 x EDURANT (rilpivirine 25 mg) tablet under moderate-fat fed conditions ([~625 kcal: 125 kcal from protein (20%), 300 kcal from carbohydrate (48%), and 200 kcal from fat (32%)]). The study was conducted in healthy, adult male and female subjects (n=118).

TIVICAY (50 mg dolutegravir) tablets and EDURANT (25 mg rilpivirine) tablets administered as reference products in the study are comparable to the commercial marketed products.

The JULUCA (50 mg dolutegravir/25 mg rilpivirine) fixed dose combination tablet was bioequivalent to TIVICAY (dolutegravir 50 mg) tablets plus EDURANT (rilpivirine 25 mg) tablets co-administered as separate tablets after a moderate-fat meal. The results from 113 subjects are presented below.

Table 12 Summary of the Comparative Bioavailability Data for Dolutegravir

Dolutegravir (1 x 50 mg) MODERATE-FAT FED CONDITIONS From measured data Geometric Mean[5] Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**Ratio of Geometric Means in %**	**90% Confidence Interval**
AUC_T (ng.h/mL)	63583.4 65510.8 (24)	61265.4 63225.3 (26)	103.8	(101.1, 106.6)
AUC_I (ng.h/mL)	64967.8 66881.9 (24)	62654.9 64606.8 (25)	103.7	(101.0, 106.4)
C_{MAX} (ng/mL)	3646.0 3703.3 (17)	3473.9 3534.4 (19)	105.0	(102.2, 107.8)
T_{MAX}[3] (h)	3.0 (0.5, 6.0)	3.0 (0.5, 8.0)		
$T_{½}$[4] (h)	14.8 (21)	15.1 (21)		

1 JULUCA (50 mg dolutegravir/25 mg rilpivirine) fixed-dose combination tablets.
2 TIVICAY (50 mg dolutegravir) and EDURANT (25 mg rilpivirine) tablets administered concurrently.
3 Expressed as median (range).
4 Expressed as the arithmetic mean (CV%) only.
5 Adjusted geometric mean

Table 13 Summary of the Comparative Bioavailability Data for Rilpivirine

Rilpivirine (1 x 25 mg) MODERATE-FAT FED CONDITIONS From measured data Geometric Mean[7] Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**Ratio of Geometric Means in %**	**90% Confidence Interval**
AUC_{0-72} (ng.h/mL)	2016.6 2125.7 (31)	1834.8 1948.9 (35)	109.9	(103.7, 116.5)
AUC_I (ng.h/mL)	3248.0[5]	2932.5[5]	110.8	(104.5, 117.4)
	3254.4[6] 3521.1 (40)	2936.0[6] 3183.8 (41)	110.8	(104.6, 117.5)
C_{MAX} (ng/mL)	93.3 100.1 (34)	83.0 88.4 (34)	112.4	(104.7, 120.7)
T_{MAX}[3] (h)	4.0 (1.0, 9.0)	4.0 (1.5, 9.0)		
$T_{½}$[4] (h)	55.8 (39)	56.9 (44)		

1 JULUCA (50 mg dolutegravir/25 mg rilpivirine) fixed-dose combination tablets.
2 TIVICAY (50 mg dolutegravir) and EDURANT (25 mg rilpivirine) tablets administered concurrently.
3 Expressed as median (range)
4 Expressed as the arithmetic mean (CV%) only.
5 For AUC_I, 1 subject was excluded from both periods due to a result "not determined" in reference treatment; in a separate supportive analysis this subject's test treatment AUC (0-∞) was included
6 Adjusted geometric mean

14 MICROBIOLOGY

Antiviral Activity in cell culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.51 nM to 2.1 nM in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.

When dolutegravir was tested in PBMC assays against a panel consisting of 24 HIV-1 clinical isolates [group M (clades 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 (0.02 to 2.14 nM) for HIV-1, while the geometric mean EC_{50} was 0.18 nM (0.09 to 0.61nM) 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/mL).

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 following drugs were not antagonistic with dolutegravir in *in vitro* assessments conducted in checkerboard format: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc, adefovir and raltegravir. In addition, the anti-HCV drug ribavirin had 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 0.064 μg/mL. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve patients 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
In the pooled SWORD-1 and SWORD-2 trials, 2 subjects in each treatment arm had confirmed virologic failure at any time through Week 48. The 2 subjects in the dolutegravir/rilpivirine arm had detectable resistance substitutions at rebound. One subject had the NNRTI-resistance-associated substitution K101K/E with no decreased susceptibility to rilpivirine (fold-change = 1.2) at Week 36, had no INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir (fold-change less than 2), and had HIV-1 RNA less than 50 copies per mL at the withdrawal visit. The other subject had the dolutegravir resistance-associated substitution G193E at baseline (by exploratory HIV proviral DNA archive sequencing) and Week 24 (by conventional sequencing) without decreased susceptibility to dolutegravir (fold-change = 1.02) at Week 24. No resistance-associated substitutions were observed for the other 2 subjects in the comparative current antiretroviral regimen arms.

Treatment-naïve HIV-1-infected patients on Dolutegravir: Please refer to the TIVICAY product monograph.

Treatment-naïve HIV-1-infected patients on Rilpivirine: Please refer to the EDURANT product monograph.

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.

Cross-resistance to efavirenz, etravirine, and/or nevirapine is likely after virologic failure and development of rilpivirine resistance.

Recombinant Resistant 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.

15 NON-CLINICAL TOXICOLOGY

General Toxicology

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).

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 and Developmental Toxicology

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). In a non-clinical distribution study in animals, dolutegravir was shown to cross the placenta.

Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function with rilpivirine. There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-fetal 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.

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, a dose that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

16 SUPPORTING PRODUCT MONOGRAPHS

1. EDURANT (tablets, 25 mg rilpivirine), submission control #185031, Product Monograph, Janssen Inc. (May 10, 2016)
2. TIVICAY (tablets, 10, 25, and 50 mg dolutegravir), submission control #192462, Product Monograph, ViiV Healthcare ULC. (Feb., 03, 2017).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

JULUCA
50 mg Dolutegravir / 25 mg Rilpivirine Tablets

Read this carefully before you start taking **JULUCA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **JULUCA**.

What is JULUCA used for?
- JULUCA is used to treat HIV (human immunodeficiency virus) infection in adults
- JULUCA replaces your current HIV treatment.

How does JULUCA work?
JULUCA contains two medicines that are used to treat HIV infection: Dolutegravir and Rilpivirine.

These medicines work together to keep the amount of virus in your body at a low level. This helps maintain the number of CD4+ cell count in your blood. CD4+ cells are a type of white blood cells that are important in helping your body to fight infection. JULUCA does not cure HIV infection.

What are the ingredients in JULUCA?
Medicinal ingredients: 50 mg dolutegravir (as dolutegravir sodium), 25 mg rilpivirine (as rilpivirine hydrochloride).
Non-medicinal ingredients: croscarmellose sodium, D-mannitol, iron oxide red, iron oxide yellow, lactose monohydrate, macrogol/PEG, magnesium stearate, microcrystalline cellulose, polysorbate 20, polyvinyl alcohol-part hydrolyzed, povidone K29/32 and K30, silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, talc, titanium dioxide

JULUCA comes in the following dosage form:
50 mg dolutegravir / 25 mg rilpivirine fixed dose combination tablets.

Do not use JULUCA if:
- You are allergic *(hypersensitive)* to dolutegravir (TIVICAY or TRIUMEQ) or rilpivirine (COMPLERA, EDURANT, or ODEFSEY) or to any of the other ingredients of JULUCA. See "What are the ingredients in JULUCA?".
- You are taking any of these medicines:
  - dofetilide (to treat heart conditions).
  - carbamazepine, oxcarbazepine, phenobarbital, or phenytoin (also known as anticonvulsants used to treat epilepsy and prevent seizures).
  - rifampin or rifapentine (to treat some bacterial infections such as tuberculosis).
  - omeprazole, esomeprazole, lansoprazole, pantoprazole, or rabeprazole (proton pump inhibitors that are medicines to prevent and treat stomach ulcers, heartburn or acid reflux disease).

- Dexamethasone – more than one dose (a corticosteriod used in a variety of conditions such as inflammation and allergic reactions).
- products that contain St John's wort (*Hypericum perforatum*) (a herbal product used to treat depression).

Don't take JULUCA with any of these medicines. Talk to your Healthcare professional first.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take JULUCA. Talk about any health conditions or problems you may have, including if you:

- have ever had a mental health problem.
- have had liver problems, including hepatitis B or C infection.
- have ever had a severe skin rash or an allergic reaction to dolutegravir (TIVICAY or TRIUMEQ) or rilpivirine (COMPLERA, EDURANT, or ODEFSEY).
- are pregnant or plan to become pregnant. It is not known if JULUCA will harm your unborn baby.
  - There is a registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare professional about how you can take part in this registry.
- could get pregnant. While taking JULUCA, use a reliable method of contraception to prevent pregnancy.
- are breastfeeding or plan to breastfeed because of the risk of passing HIV-1 to your baby. Talk with your healthcare provider about the best way to feed your baby. It is not known whether the ingredients of JULUCA can pass into breast milk and harm your baby. If you are taking JULUCA, do not breastfeed.

Other warnings you should know about:

JULUCA will not stop you from passing HIV to others. You should take steps to avoid this by:

- Using condoms when you have oral or penetrative sex.
- Not reusing or sharing needles, syringes, or other injection equipment.

Serious liver problems including liver injury and liver failure have been seen in people taking medicines containing dolutegravir (see **Serious side effects and what to do about them**). In some cases the liver injury has led to a liver transplant. While you are being treated with JULUCA your doctor will monitor you closely for any signs of liver problems.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with JULUCA:

- metformin, to treat diabetes.
- medicines called antacids to treat indigestion and heartburn or laxatives, or other products that contain aluminum and/or calcium carbonate, magnesium or buffered medicines.
  - Taking antacids can stop JULUCA from being absorbed into your body and not make it work as well.
  - JULUCA should be taken at least 4 hours before or 6 hours after you take an antacid.
- calcium and iron supplements (non-antacids).
  - Taking these supplements can stop JULUCA from being absorbed into your body and not make it work as well.

    - Supplements containing calcium or iron can be taken at the same time as JULUCA and a meal.
    - Otherwise, JULUCA should be taken at least 4 hours before or 6 hours after you take these supplements.
- famotidine, cimetidine, nizatidine, and ranitidine (H_2-receptor antagonists) to treat indigestion and heartburn
    - H_2-receptor antagonists can stop JULUCA from being absorbed into your body and make it not work as well.
    - JULUCA should be taken at least 4 hours before or 12 hours after you take a H_2-receptor antagonist.
- rifabutin, to treat some bacterial infections, such as tuberculosis (TB)
    - if you take rifabutin, your doctor will also need to give you a dose of Edurant (rilpivirine).
    - Your healthcare professional will give you advice on how to take rifabutin with JULUCA.
- clarithromycin, erythromycin, antibiotics used to treat bacterial infections.
- methadone, a medicine used to treat narcotic withdrawal and dependence.
- efavirenz, etravirine, and nevirapine (non-nucleoside reverse transcriptase inhibitors [NNRTIs]) to treat HIV infection.
- any other medicine to treat HIV infection.

Talk to your healthcare professional for further advice if you are taking any of these medicines.

How to take JULUCA:
Always take JULUCA every day with a meal exactly as your doctor has told you to. Check with your healthcare professional if you're not sure.

- Taking JULUCA with a meal is important to help get the right amount of medicine in your body. A protein drink alone (or meal replacement drink) does not replace a meal.

Usual dose:
The usual dose of JULUCA is one tablet (50 mg dolutegravir and 25 mg rilpivirine) taken once a day with a meal.

Take JULUCA for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

Overdose:

If you think you have taken too much JULUCA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take JULUCA with a meal as soon as you remember. If your next dose is due within 12 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before. Don't take a double dose to make up for a missed dose.

What are possible side effects from using JULUCA?

These are not all the possible side effects you may feel when taking JULUCA. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of JULUCA are:

- Headache
- Diarrhea

Additional side effects that may occur include: decreased appetite, intestinal gas (wind/flatulence), stomach pain/discomfort, feeling sick (nausea), being sick (vomiting), abnormal dreams, difficulty falling asleep or staying asleep, weight gain, dizziness and/or itching.

Tell your doctor if you have any side effect that bothers you or that does not go away. For more information, ask your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Severe skin rash and allergic (hypersensitivity) reactions: • Skin rash, fever, lack of energy (fatigue), swelling of the mouth or face causing difficulty in breathing, blisters or sores in mouth, muscle or joint aches			✓
Depression or mood changes: • Feelings of deep sadness • Feelings of unworthiness • Have thoughts of hurting yourself (suicide) • Have tried to hurt yourself (behavior) • Anxiety; feelings of worry, nervousness or unease.		✓ ✓ ✓ ✓ ✓	
Liver problems and blood test results: • Inflammation (Hepatitis) • Bilirubin increase (substance produced by liver) • Increase of muscle enzymes (CPK, creatinine)		✓ ✓ ✓	
RARE			
Liver failure: • Extremely high liver		✓	

blood test results • Yellowing of the skin and the whites of the eyes • Dark or tea coloured urine • Pale coloured stools/ bowel movements • Nausea/ vomiting • Loss of appetite • Pain, aching or tenderness on right side below the ribs		✓ ✓ ✓ ✓ ✓ ✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store JULUCA up to 30°C
- Store JULUCA tablets in the original bottle. Keep the bottle tightly closed and protected from moisture.
- The bottle of JULUCA contains a silica gel desiccant to help keep your medicine dry and protect it from moisture. Do not remove the desiccant from the bottle.

Keep out of reach and sight of children.

Proper disposal:
Don't throw away any medicines down the drain, household waste or flushed in the toilet. Give all unused medicines to your local pharmacy for proper disposal. This will help to protect the environment.

If you want more information about JULUCA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website

(http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.viivhealthcare.ca, or by calling 1-877-393-8448.

This leaflet was prepared by ViiV Healthcare ULC.

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