Brand Name	Juluca
Active Ingredient(s)	dolutegravir, rilpivirine
Strength	50-25 mg
Dosage Form	tablet
Inactive 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
NDC	49702-242-13
DIN	02475774
Canadian Distributor	ViiV Healthcare ULC 1400 75 Rue Queen, Montreal, Quebec, Canada H3C 2N6
NDA Number	NDA210192
US Distributor (NDA Holder)	ViiV Healthcare 5 Moore Drive, Research Triangle Park, North Carolina USA 27709
Manufacturer (Final Packager)	GlaxoSmithKline Durham, NC 27701
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JULUCA safely and effectively. See full prescribing information for JULUCA.

JULUCA (dolutegravir and rilpivirine tablets), for oral use
Initial U.S. Approval: 2017

---------- INDICATIONS AND USAGE----------
JULUCA, a two-drug combination of dolutegravir, an HIV-1 integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those 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 treatment failure and no known substitutions associated with resistance to the individual components of JULUCA. (1)

----------DOSAGE AND ADMINISTRATION----------
- Pregnancy Testing: Pregnancy testing is recommended before initiation of JULUCA in individuals of childbearing potential. (2.1, 5.3, 8.1, 8.3)
- One tablet taken orally once daily with a meal. (2.2)
- Rifabutin coadministration: Take an additional 25-mg tablet of rilpivirine with JULUCA once daily with a meal for the duration of the rifabutin coadministration. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
Each tablet contains: 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride). (3)

---------- CONTRAINDICATIONS ----------
- Previous hypersensitivity reaction to dolutegravir or rilpivirine. (4)
- Coadministration with dofetilide. (4)
- Coadministration with drugs where significant decreases in rilpivirine plasma concentrations may occur, which may result in loss of virologic response. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Severe skin and hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported with the individual components. Discontinue JULUCA immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)
- Hepatotoxicity has been reported in patients receiving a dolutegravir- or rilpivirine-containing regimen. Monitoring for hepatotoxicity is recommended. (5.2)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of JULUCA and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Individuals of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.3, 8.1, 8.3)
- Depressive disorders have been reported with the use of rilpivirine- or dolutegravir-containing regimens. Immediate medical evaluation is recommended for severe depressive symptoms. (5.4, 6.1)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (all grades) observed in at least 2% of subjects were diarrhea, headache, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
- Because JULUCA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Refer to the full prescribing information for important drug interactions with JULUCA. (4, 5.4, 7)
- Drugs that induce or inhibit cytochrome P450 (CYP)3A4 or uridine diphosphate glucuronosyltransferase (UGT)1A1 may affect the plasma concentrations of the components of JULUCA. (7.3)
- Drugs that increase gastric pH or containing polyvalent cations may decrease plasma concentrations of the components of JULUCA. (4, 7.3, 7.4)
- Consider alternatives to prescribing JULUCA with drugs with a known risk of Torsade de Pointes. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Assess the risks and benefits of JULUCA and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1, 8.3)
- Rilpivirine exposure during pregnancy: Total rilpivirine exposures were generally lower during pregnancy compared with the postpartum period. (8.1, 12.3).
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in individuals of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

JULUCA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those 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 treatment failure and no known substitutions associated with resistance to the individual components of JULUCA.

2 DOSAGE AND ADMINISTRATION

2.1 Pregnancy Testing before Initiation of JULUCA

Pregnancy testing is recommended before initiation of JULUCA in individuals of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage

The recommended dosage of JULUCA is one tablet taken orally once daily with a meal *[see Clinical Pharmacology (12.3)]*. One tablet of JULUCA contains 50 mg of dolutegravir and 25 mg of rilpivirine.

2.3 Recommended Dosage with Rifabutin Coadministration

If JULUCA is coadministered with rifabutin, take an additional 25-mg tablet of rilpivirine with JULUCA once daily with a meal for the duration of the rifabutin coadministration *[see Drug Interactions (7.4)]*.

3 DOSAGE FORMS AND STRENGTHS

JULUCA tablets are pink, oval, biconvex tablets debossed with “SV J3T” on one side. Each film-coated tablet contains 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride).

4 CONTRAINDICATIONS

JULUCA is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir or rilpivirine *[see Warnings and Precautions (5.1)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7)]*.
- receiving other coadministered drugs in Table 1 that significantly decrease rilpivirine plasma concentrations *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Table 1. Drugs That are Contraindicated with JULUCA

Drug Class	Contraindicated Drugs in Class	Clinical Comment
Antiarrhythmic	Dofetilide	Potential for serious and/or life-threatening events due to the potential for increased dofetilide plasma concentrations.
Anticonvulsants	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Potential for significant decreases in rilpivirine plasma concentrations due to cytochrome P450 (CYP)3A enzyme induction, which may result in loss of virologic response.
Antimycobacterials	Rifampin Rifapentine	
Glucocorticoid (systemic)	Dexamethasone (more than a single-dose treatment)	
Herbal Products	St John's wort (*Hypericum perforatum*)	
Proton Pump Inhibitors	e.g., Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	Potential for significant decreases in rilpivirine plasma concentrations due to gastric pH increase, which may result in loss of virologic response.

5 WARNINGS AND PRECAUTIONS

5.1 Skin and Hypersensitivity Reactions

Hypersensitivity reactions have been reported with dolutegravir and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. These events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials.

Severe skin and hypersensitivity reactions have been reported during postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. 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 subjects. No Grade 4 rash was reported *[see Adverse Reactions (6.2)]*.

Discontinue JULUCA 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 after the onset of hypersensitivity may result in a life-threatening reaction *[see Contraindications (4)]*.

5.2 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir- or rilpivirine-containing regimen *[see Adverse Reactions (6.1)]*. 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.

5.3 Embryo-Fetal Toxicity

An ongoing observational study showed 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. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform individuals of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with JULUCA. Assess the risks and benefits of JULUCA and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester *[see Use in Specific Populations (8.1. 8.3)]*.

Pregnancy testing is recommended before initiation of JULUCA in individuals of childbearing potential *[see Dosage and Administration (2.1)]*.

Individuals of childbearing potential should be counseled on the consistent use of effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

JULUCA may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.4 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 *[see Adverse Reactions (6.1)]*. For information regarding depressive disorders reported in patients taking dolutegravir, *see Adverse Reactions (6.1)*. 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.

5.5 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 (4), Drug Interactions (7.4)]:*

- 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 of 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 Drug Interactions (7.3), Clinical Pharmacology (12.2)]*. 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.

6 ADVERSE REACTIONS

The following adverse reactions are described below and in other sections of the labeling:

- Skin and hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*.
- Depressive disorders *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of JULUCA is based on the pooled primary Week 48 analyses of data from 2 identical, international, multicenter, open-label trials, SWORD-1 and SWORD-2, including additional follow up through Week 148.

A total of 1,024 adult HIV-1–infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 nucleoside reverse transcriptase inhibitors [NRTIs] plus either an integrase strand transfer inhibitor [INSTI], a non-nucleoside reverse transcriptase inhibitor [NNRTI], or a protease inhibitor [PI]) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine, were randomized and received treatment. Subjects were randomized 1:1 to continue their current antiretroviral regimen or be switched to dolutegravir plus rilpivirine administered once daily. Subjects originally assigned to continue their current antiretroviral regimen and who remained virologically suppressed at Week 48 switched to dolutegravir plus rilpivirine at Week 52. In the pooled analyses, the proportion of subjects who discontinued treatment due to an adverse event through Week 48 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 through Week 48 were psychiatric disorders: 2% of subjects receiving dolutegravir plus rilpivirine and less than 1% on the current antiretroviral regimen. In the pooled analyses, the proportion of subjects receiving dolutegravir plus rilpivirine who discontinued treatment due to an adverse event through Week 148 was 8%.

The most common adverse reactions (ARs) (all grades) reported in at least 2% of subjects in the Week 48 pooled analyses from SWORD-1 and SWORD-2 are provided in Table 2.

Table 2. Adverse Reactions (Grades 1 to 4) Reported in at Least 2% of Virologically Suppressed Subjects with HIV-1 Infection in SWORD-1 and SWORD-2 Trials (Week 48 Pooled Analyses)

Adverse Reaction	Dolutegravir plus Rilpivirine (n = 513)	Current Antiretroviral Regimen (n = 511)
Diarrhea	2%	<1%
Headache	2%	0

In the Week 148 pooled analyses, the only adverse reaction (all grades) occurring in at least 2% of subjects who received dolutegravir plus rilpivirine and that was not observed during the Week 48 analyses was nausea (2%).

Less Common Adverse Reactions

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

General Disorders: Fatigue.

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

Hepatobiliary Disorders: Cholecystitis, cholelithiasis, hepatitis.

Immune System Disorders: Immune reconstitution syndrome.

Metabolism and Nutrition Disorders: Decreased appetite.

Musculoskeletal Disorders: Myositis.

Nervous System Disorders: Dizziness, somnolence.

Psychiatric Disorders: Depressive disorders including depressed mood; depression; suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness. Other reported psychiatric adverse reactions include anxiety, insomnia, sleep disorders, and abnormal dreams.

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

Skin and Subcutaneous Tissue Disorders: Pruritus, rash.

Laboratory Abnormalities

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in the Week 48 pooled analysis are presented in Table 3.

Table 3. Selected Laboratory Abnormalities (Grades 2 and 3 to 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) Grade 3 to 4 (≥10.0 x ULN)	 <1% 1%	 <1% 2%
Hyperglycemia Grade 2 (126-250 mg/dL) Grade 3 to 4 (>250 mg/dL)	 4% <1%	 5% <1%
Lipase Grade 2 (>1.5-3.0 x ULN) Grade 3 to 4 (>3.0 x ULN)	 5% 2%	 5% 2%

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal.

In the Week 148 pooled analyses, there were no additional selected laboratory abnormalities with dolutegravir plus rilpivirine compared with those shown in Table 3.

Changes in Serum Creatinine: Dolutegravir and rilpivirine have been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment with dolutegravir plus rilpivirine and remained stable through 148 weeks. Mean changes from baseline of 0.093 mg per dL (range: -0.30 to 0.58 mg per dL) and 0.112 mg per dL (range: -0.24 to 0.81 mg per dL) were observed after 48 and 148°weeks of treatment with dolutegravir plus rilpivirine, respectively. These changes are not considered to be clinically relevant.

Serum Lipids: At 48 weeks, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol to HDL ratio were similar between the treatment arms, with no further notable changes beyond Week 48.

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) 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. In subjects who received dolutegravir plus rilpivirine from study start and were continuing JULUCA at Week 148, mean BMD increases from baseline were 0.98% (total hip) and 0.53% (lumbar spine). 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving a dolutegravir- or rilpivirine-containing regimen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Investigations

Weight increased.

Musculoskeletal Disorders

Arthralgia, myalgia.

Renal and Genitourinary Disorders

Nephrotic syndrome.

Skin and Subcutaneous Tissue Disorders

Severe skin and hypersensitivity reactions, including DRESS.

7 DRUG INTERACTIONS

7.1 Concomitant Use with Other Antiretroviral Medicines

Because JULUCA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended *[see Indications and Usage (1)]*. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided *[see Contraindications (4), Warnings and Precautions (5.5), Clinical Pharmacology (12.3)]*.

7.2 Potential for JULUCA to Affect Other Drugs

Dolutegravir, a component of JULUCA, inhibits the renal organic cation transporters (OCT)2 and multidrug and toxin extrusion transporter (MATE)1, thus it may increase plasma

concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide, dalfampridine, and metformin *[see Contraindications (4), Drug Interactions (7.4)]*.

7.3 Potential for Other Drugs to Affect the Components of JULUCA

Dolutegravir

Dolutegravir is metabolized by uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 with some contribution from cytochrome P450 (CYP)3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir *[see Drug Interactions (7.4)]*. Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

Coadministration of dolutegravir with polyvalent cation-containing products may lead to decreased absorption of dolutegravir *[see Drug Interactions (7.4)]*.

Rilpivirine

Rilpivirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of rilpivirine. Coadministration of JULUCA and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs *[see Contraindications (4), Drug Interactions (7.4)]*. Coadministration of JULUCA and drugs 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 *[see Contraindications (4), Drug Interactions (7.4), Clinical Pharmacology (12.3)]*.

QT-Prolonging Drugs: In healthy subjects, 75 mg once daily of 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 Clinical Pharmacology (12.2)]*. Consider alternatives to JULUCA when coadministered with a drug with a known risk of Torsade de Pointes.

7.4 Established and Other Potentially Significant Drug Interactions

Information regarding potential drug interactions with dolutegravir and rilpivirine are provided in Table 4. These recommendations are based on either drug interaction trials of individual components or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy *[see Contraindications (4), Warnings and Precautions (5.5), Clinical Pharmacology (12.3)].*

Table 4. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions[a]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antacids (e.g., aluminum or magnesium hydroxide, calcium carbonate)	↓Rilpivirine	Administer JULUCA 4 hours before or 6 hours after taking antacids.
Antiarrhythmic: Dofetilide	↑Dofetilide	Coadministration is contraindicated with JULUCA *[see Contraindications (4)]*.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓Dolutegravir ↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.
Antidiabetic: Metformin[b]	↑Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use of JULUCA and metformin.
Antimycobacterials: Rifampin Rifapentine	↓Dolutegravir ↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.
Antimycobacterial: Rifabutin[b]	↔Dolutegravir ↔Rifabutin ↓Rilpivirine	An additional rilpivirine 25-mg tablet should be taken with JULUCA once daily with a meal when rifabutin is coadministered.
Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment)	↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.
H_2-receptor antagonists: Famotidine Cimetidine Nizatidine Ranitidine	↔Dolutegravir ↓Rilpivirine	JULUCA should only be administered at least 4 hours before or 12 hours after taking H_2-receptor antagonists.

Herbal product: St John's wort (*Hypericum perforatum*)	↓ Dolutegravir ↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.
Macrolide or ketolide antibiotics: Clarithromycin Erythromycin Telithromycin	↔Dolutegravir ↑Rilpivirine	Where possible, consider alternatives, such as azithromycin.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing products[b] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer JULUCA 4 hours before or 6 hours after taking products containing polyvalent cations.
Narcotic analgesic: Methadone[b]	↔Dolutegravir ↓Methadone ↔Rilpivirine	No dose adjustments are required when starting coadministration of methadone with JULUCA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Oral calcium and iron supplements, including multivitamins containing calcium or iron[b] (non-antacid)	↓Dolutegravir	Administer JULUCA and supplements containing calcium or iron together with a meal or take JULUCA 4 hours before or 6 hours after taking these supplements.
Potassium channel blocker: Dalfampridine	↑Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with JULUCA should be considered against the risk of seizures in these patients.
Proton pump inhibitors: e.g., Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.

↑ = Increase, ↓ = Decrease, ↔ = No change.

[a] This table is not all inclusive.
[b] *See Clinical Pharmacology (12.3) for magnitude of interaction.*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to JULUCA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Data from an ongoing birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir, a component of JULUCA, is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise individuals of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with use of JULUCA. Assess the risks and benefits of JULUCA and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development *[see Warnings and Precaution (5.3)]*.

There are insufficient human data on the use of JULUCA during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. 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 recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of JULUCA at systemic exposures (AUC) to dolutegravir less than (rabbits) and 38 times (rats) and exposures to rilpivirine 15 (rats) and 70 (rabbits) times the exposure at the recommended human dose (RHD) of JULUCA *(see Data)*.

Data

Human Data: Dolutegravir: In a birth outcome surveillance study in Botswana, there were 7 cases of neural tube defects reported out of 3,591 deliveries (0.19%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural

tube defect prevalence rates were 0.11% (21/19,361 deliveries) in the non-dolutegravir arm and 0.07% (87/119,630 deliveries) in the HIV-uninfected arm. Seven cases reported with dolutegravir included 3 cases of myelomeningocele, 2 cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, no increased risk of neural tube defects was identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 5 infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy. The reported risks of neural tube defects by treatment groups were based on interim analyses from the ongoing surveillance study in Botswana. It is unknown if baseline characteristics were balanced between the study treatment groups. The observed trends of association could change as data accumulate.

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to definitively address the risk of neural tube defects with dolutegravir.

Data from the birth outcome surveillance study described above and postmarketing sources with more than 1,000 pregnancy outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) following second-/third-trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

Dolutegravir has been shown to cross the placenta. In a clinical trial in Uganda and South Africa in women during the last trimester of pregnancy receiving dolutegravir 50 mg once daily, the ratio of median dolutegravir concentration in fetal umbilical cord to that in maternal peripheral plasma was 1.21 (range 0.51-2.11) (n = 15).

Rilpivirine: Based on prospective reports to the APR of over 610 exposures to rilpivirine-containing regimens during pregnancy resulting in live births (including over 420 exposed during the first trimester and over 190 exposed in the second/third trimester), there was no significant difference between the overall risk of birth defects for rilpivirine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 1.4% (95% CI: 0.5% to 3.0%) and 1.6% (95% CI: 0.3% to 4.5%) following first and second/third trimester exposure, respectively, to rilpivirine-containing regimens.

Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 HIV-1–infected pregnant subjects during the second and third trimesters and postpartum. Each of the subjects were on a rilpivirine-based regimen at the time of enrollment. Twelve subjects

completed the trial through the postpartum period (6 to 12 weeks after delivery) and pregnancy outcomes are missing for 6 subjects. The exposure (C_{0h} and AUC) of total rilpivirine was approximately 30% to 40% lower during pregnancy compared with postpartum (6 to 12 weeks). The protein binding of rilpivirine was similar (>99%) during the second trimester, third trimester, and the postpartum period *[see Clinical Pharmacology (12.3)]*. One subject discontinued the trial following fetal death at 25 weeks' gestation due to suspected premature rupture of membranes. Among the 12 subjects who were virologically suppressed at baseline (less than 50 copies/mL), virologic response was preserved in 10 subjects (83.3%) through the third trimester visit and in 9 subjects (75%) through the 6- to 12-week postpartum visit. Virologic outcomes during the third trimester visit were missing for 2 subjects who were withdrawn (one subject was nonadherent to the study drug and one subject withdrew consent). Among the 10 infants with HIV test results available, born to 10 HIV-1–infected pregnant subjects, all had negative test results for HIV-1 at the time of delivery and up to 16 weeks postpartum. All 10 infants received antiretroviral prophylactic treatment with zidovudine. 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.

Animal Data: Dolutegravir: Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on Gestation Days 6 to 17 and 6 to 18, respectively, and to rats on Gestation Day 6 to Lactation/Post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans, and in rats were approximately 38 times the exposure in humans (50 mg once daily). In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 32 times the human exposure with 50 mg once daily).

Rilpivirine: Rilpivirine was administered orally to pregnant rats (40, 120, or 400 mg per kg per day) and rabbits (5, 10, or 20 mg per kg per day) through organogenesis (on Gestation Days 6 through 17, and 6 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with rilpivirine in rats and rabbits at exposures 15 (rats) and 70 (rabbits) times higher than the exposure in humans at the recommended dose of 25 mg once daily. In a pre/postnatal development study with rilpivirine, where rats were administered up to 400 mg per kg per day through lactation, no significant adverse effects directly related to drug were noted in the offspring.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Dolutegravir is present in human milk. It is not known whether JULUCA or components of JULUCA affect human milk production or have effects on the breastfed infant. When administered to lactating rats, rilpivirine was present in milk *(see Data)*.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving JULUCA.

Data

Animal Data: Rilpivirine: In animals, no studies have been conducted to assess the excretion of rilpivirine into milk directly; however, rilpivirine was present in plasma of rat pups exposed through the milk of lactating rats (dosed up to 400 mg per kg per day).

8.3 Females and Males of Reproductive Potential

In individuals of childbearing potential currently on JULUCA who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing JULUCA and discuss with the patient if an alternative treatment should be considered *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended in individuals of childbearing potential before initiation of JULUCA *[see Dosage and Administration (2.1)]*.

Contraception

Individuals of childbearing potential who are taking JULUCA should be counseled on the consistent use of effective contraception.

8.4 Pediatric Use

The safety and efficacy of JULUCA have not been established in pediatric patients.

8.5 Geriatric Use

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 *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dosage adjustment is necessary for patients with mild or moderate renal impairment (creatinine clearance greater than or equal to 30 mL/min) *[see Clinical Pharmacology (12.3)]*. In patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease, increased monitoring for adverse effects is recommended.

8.7 Hepatic Impairment

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir or rilpivirine is unknown *[see Clinical Pharmacology (12.3)]*.

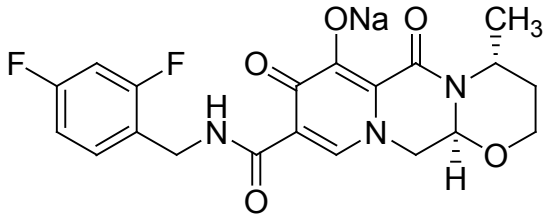
10 OVERDOSAGE

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 and ECG (QT interval) as well as observation of the clinical status of the patient. As both dolutegravir and rilpivirine are highly bound to plasma proteins, it is unlikely that either would be significantly removed by dialysis.

11 DESCRIPTION

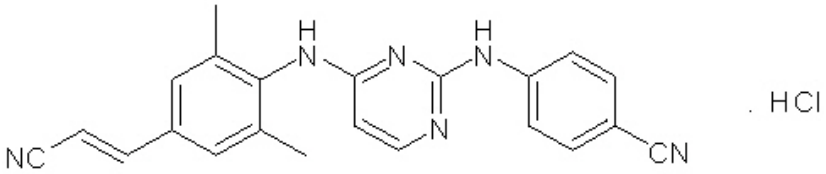
JULUCA is a fixed-dose combination tablet containing dolutegravir (as dolutegravir sodium), an INSTI, and rilpivirine (as rilpivirine hydrochloride), an NNRTI.

The chemical name of dolutegravir sodium is 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. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol. It has the following structural formula:



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

The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6$ • HCl and its molecular weight is 402.88g per mol. Rilpivirine hydrochloride has the following structural formula:



Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

JULUCA tablets are for oral administration. Each film-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride) and the inactive ingredients croscarmellose sodium, D-mannitol, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, povidone K29/32 and K30, silicified microcrystalline cellulose, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients iron oxide red, iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

JULUCA is a fixed-dose combination of the HIV-1 antiretroviral agents, dolutegravir and rilpivirine *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of JULUCA on the QT interval has not been studied.

In a randomized, placebo-controlled, crossover trial, 42 healthy subjects received single-dose oral administration 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. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours postdose.

The effect of rilpivirine at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo- and active- (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady state. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction was 2.0 (5.0) milliseconds (i.e., below the threshold of clinical concern). When 75 mg and 300 mg once daily of rilpivirine (3 times and 12 times the recommended dosage in JULUCA, respectively) 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) milliseconds, respectively. Steady-state administration of rilpivirine 75 mg once daily and 300 mg once daily resulted in a mean steady-state C_{max} approximately 2.6-fold and 6.7-fold, respectively, higher than the mean C_{max} observed with the recommended 25-mg once-daily dose of rilpivirine *[see Drug Interactions (7.4)]*.

Effects on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg

once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of JULUCA are provided in Table 5. The multiple-dose pharmacokinetic parameters are provided in Table 6.

Table 5. Pharmacokinetic Properties of the Components of JULUCA

	Dolutegravir	**Rilpivirine**
Absorption		
T_{max} (h)	3	4
Effect of moderate-fat meal (relative to fasting)[a]	AUC Ratio 1.87 (1.54, 2.26)	AUC Ratio 1.57 (1.24, 1.98)
Effect of high-fat meal (relative to fasting)[a]	AUC Ratio 1.87 (1.53, 2.29)	AUC Ratio 1.72 (1.36, 2.16)
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)	14	50
% of dose excreted as total ^{14}C (unchanged drug) in urine[b]	31 (<1)	6.5 (<1)
% of dose excreted as total ^{14}C (unchanged drug) in feces[b]	64 (53)	85 (25)

UGT = uridine diphosphate glucuronosyltransferase; CYP = Cytochrome P450.

[a] Geometric mean ratio (fed/fasted) in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~900 kcal, 56% fat. Moderate-fat meal = ~625 kcal, 32% fat. When rilpivirine was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal.

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

Table 6. Multiple-Dose Pharmacokinetic Properties of the Components of JULUCA

Parameter Mean (CV%)	Dolutegravir[a]	Rilpivirine[a]
C_{max} (mcg/mL)	3.67 (20)	0.13 (54)[b]
AUC_{tau} (mcg/h/mL)	53.6 (27)	2.2 (38)
C_{trough} (mcg/mL)	1.11 (46)	0.08 (44)

[a] Based on population pharmacokinetic analyses using pooled data from ART treatment-naïve adults receiving 50 mg dolutegravir once daily or 25 mg rilpivirine once daily.

[b] Observed C_{max} in a pharmacokinetic substudy in ART treatment-naïve adults receiving 25 mg rilpivirine once daily.

Specific Populations

Pediatric Patients: The pharmacokinetics of dolutegravir plus rilpivirine has not been studied in pediatric subjects *[see Use in Specific Populations (8.4)]*.

Geriatric Patients: Population pharmacokinetic analyses from studies with the individual components indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir or rilpivirine. Pharmacokinetic data in subjects 65 years of age and older are limited *[see Use in Specific Populations (8.5)]*.

Patients with Renal Impairment: Population pharmacokinetic analyses indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. Dolutegravir AUC, C_{max}, and C_{24} 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. There is inadequate information to recommend appropriate dosing of dolutegravir in patients requiring dialysis *[see Use in Specific Populations (8.6)]*.

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.

Patients with Hepatic Impairment: Dolutegravir exposures were similar in subjects (n = 8) with moderate hepatic impairment (Child-Pugh Score B) as compared with matched healthy controls. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

Rilpivirine exposure was 47% higher in subjects (n = 8) with mild hepatic impairment (Child-Pugh Score A) and 5% higher in subjects (n = 8) with moderate hepatic impairment (Child-Pugh Score B) compared with matched controls. The effect of severe hepatic impairment (Child-Pugh

Score C) on the pharmacokinetics of rilpivirine has not been studied *[see Use in Specific Populations (8.7)]*.

Patients with HBV/HCV Co-infection: Population pharmacokinetic analyses indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure of dolutegravir or rilpivirine. Subjects with hepatitis B co-infection were excluded from studies with dolutegravir plus rilpivirine.

Gender and Race: Population pharmacokinetic analyses from studies with the individual components revealed that gender and race had no clinically relevant effect on the pharmacokinetics of dolutegravir or rilpivirine.

Pregnancy and Postpartum: Rilpivirine: The exposure (C_{0h} and AUC_{24h}) to total rilpivirine after taking rilpivirine 25 mg once daily as part of an antiretroviral regimen was 30% to 40% lower during pregnancy (similar for the second and third trimesters) compared with postpartum (see Table 7). However, the exposure during pregnancy was not significantly different from exposures obtained in Phase 3 trials of rilpivirine-containing regimens. Based on the exposure-response relationship for rilpivirine, this decrease is not considered clinically relevant in patients who are virologically suppressed. The protein binding of rilpivirine was similar (>99%) during the second trimester, third trimester, and postpartum.

Table 7. Pharmacokinetic Results of Rilpivirine during the 2nd and 3rd Trimesters of Pregnancy and Postpartum Period[a]

Pharmacokinetics of Total Rilpivirine (mean ± SD)	Postpartum (6 to 12 Weeks) (n = 11)	2nd Trimester of Pregnancy (n = 15)	3rd Trimester of Pregnancy (n = 13)
C_{0h} (ng/mL)	111 ± 69.2	65.0 ± 23.9	63.5 ± 26.2
C_{min} (ng/mL)	84.0 ± 58.8	54.3 ± 25.8	52.9 ± 24.4
C_{max} (ng/mL)	167 ± 101	121 ±45.9	123 ± 47.5
T_{max} (h), median (range)	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC_{24h} (ng.h/mL)	2,714 ± 1,535	1,792 ± 711	1,762 ± 662

[a] Total rilpivirine exposure after administration of rilpivirine 25 mg once daily as part of an antiretroviral regimen.

Drug Interaction Studies

Drug interaction trials were conducted with dolutegravir or rilpivirine as individual components and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-gp, BCRP, bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

In vitro, dolutegravir inhibited the renal OCT2 (IC_{50} = 1.93 microM) and MATE1 (IC_{50} = 6.34 microM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide, dalfampridine, and metformin *[see Contraindications (4), Drug Interactions (7.4)]*.

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT)1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

Rilpivirine is primarily metabolized by CYP3A. Rilpivirine 25 mg once daily is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes.

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir or rilpivirine are provided in Table 4 *[see Drug Interactions (7.4)]*.

Table 8. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79 to 1.15)	_
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)

[a] The number of subjects represents the maximum number of subjects that were evaluated.

Table 9. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)

Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[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.

[c] The number of subjects represents the maximum number of subjects that were evaluated.

Table 10. Summary of Effect of Rilpivirine on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	**Dose of Rilpivirine**	**n**	**Geometric Mean Ratio (90% CI) of Coadministered Drug Pharmacokinetic Parameters with/without EDURANT No Effect = 1.00**		
			C_{max}	**AUC**	**C_{min}**
Acetaminophen 500 mg single dose	150 mg once daily[a]	16	0.97 (0.86 to 1.10)	0.91 (0.86 to 0.97)	NA
Atorvastatin 40 mg once daily 2-hydroxy-atorvastatin 4-hydroxy-atorvastatin	150 mg once daily[a]	16	1.35 (1.08 to 1.68) 1.58 (1.33 to 1.87) 1.28 (1.15 to 1.43)	1.04 (0.97 to 1.12) 1.39 (1.29 to 1.50) 1.23 (1.13 to 1.33)	0.85 (0.69 to 1.03) 1.32 (1.10 to 1.58) NA
Chlorzoxazone 500 mg single dose taken 2 hours after rilpivirine	150 mg once daily[a]	16	0.98 (0.85 to 1.13)	1.03 (0.95 to 1.13)	NA
Digoxin 0.5 mg single dose	25 mg once daily	22	1.06 (0.97 to 1.17)	0.98 (0.93 to 1.04)[c]	NA
Ethinylestradiol 0.035 mg once daily Norethindrone 1 mg once daily	25 mg once daily	17	1.17 (1.06 to 1.30) 0.94 (0.83 to 1.06)	1.14 (1.10 to 1.19) 0.89 (0.84 to 0.94)	1.09 (1.03 to 1.16) 0.99 (0.90 to 1.08)
Ketoconazole 400 mg once daily	150 mg once daily[a]	14	0.85 (0.80 to 0.90)	0.76 (0.70 to 0.82)	0.34 (0.25 to 0.46)
Methadone 60-100 mg once daily, individualized dose R(-) methadone	25 mg once daily	13	0.86 (0.78 to 0.95)	0.84 (0.74 to 0.95)	0.78 (0.67 to 0.91)

S(+) methadone			0.87 (0.78 to 0.97)	0.84 (0.74 to 0.96)	0.79 (0.67 to 0.92)
Metformin 850 mg single dose	25 mg once daily	20	1.02 (0.95 to -1.10)	0.97 (0.90 to 1.06)[b]	NA
Omeprazole 20 mg once daily	150 mg once daily[a]	15	0.86 (0.68 to 1.09)	0.86 (0.76 to 0.97)	NA
Rifampin 600 mg once daily 25-desacetylrifampin	150 mg once daily[a]	16	1.02 (0.93 to 1.12) 1.00 (0.87 to 1.15)	0.99 (0.92 to 1.07) 0.91 (0.77 to 1.07)	NA NA
Sildenafil 50 mg single dose *N*-desmethyl-sildenafil	75 mg once daily[a]	16	0.93 (0.80 to 1.08) 0.90 (0.80 to 1.02)	0.97 (0.87 to 1.08) 0.92 (0.85 to 0.99)[c]	NA NA
Simeprevir 150 mg once daily	25 mg once daily	21	1.10 (0.97 to 1.26)	1.06 (0.94 to 1.19)	0.96 (0.83 to 1.11)

n = Maximum number of subjects 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 coadministered drug.

[b] N (maximum number of subjects with data) for $AUC_{(0-\infty)}$ = 15.

[c] $AUC_{(0\text{-last})}$.

Table 11. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Rilpivirine

Coadministered Drug(s) and Dose(s)	**Dose of Rilpivirine**	**n**	**Geometric Mean Ratio (90% CI) of Rilpivirine Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00**		
			C_{max}	**AUC**	**C_{min}**
Acetaminophen 500 mg single dose	150 mg once daily[a]	16	1.09 (1.01 to 1.18)	1.16 (1.10 to 1.22)	1.26 (1.16 to 1.38)
Atorvastatin 40 mg once daily	150 mg once daily[a]	16	0.91 (0.79 to 1.06)	0.90 (0.81 to 0.99)	0.90 (0.84 to 0.96)
Chlorzoxazone 500 mg single dose taken 2 hours after rilpivirine	150 mg once daily[a]	16	1.17 (1.08 to 1.27)	1.25 (1.16 to 1.35)	1.18 (1.09 to 1.28)
Ethinylestradiol/ Norethindrone 0.035 mg once daily/ 1 mg once daily	25 mg once daily	15	↔[b]	↔[b]	↔[b]
Famotidine 40 mg single dose taken 12 hours before rilpivirine	150 mg single dose[a]	24	0.99 (0.84 to 1.16)	0.91 (0.78 to 1.07)	NA

Famotidine 40 mg single dose taken 2 hours before rilpivirine	150 mg single dose[a]	23	0.15 (0.12 to 0.19)	0.24 (0.20 to 0.28)	NA
Famotidine 40 mg single dose taken 4 hours after rilpivirine	150 mg single dose[a]	24	1.21 (1.06 to 1.39)	1.13 (1.01 to 1.27)	NA
Ketoconazole 400 mg once daily	150 mg once daily[b]	15	1.30 (1.13 to 1.48)	1.49 (1.31 to 1.70)	1.76 (1.57 to 1.97)
Methadone 60-100 mg once daily, individualized dose	25 mg once daily	12	↔[b]	↔[b]	↔[b]
Omeprazole 20 mg once daily	150 mg once daily[a]	16	0.60 (0.48 to 0.73)	0.60 (0.51 to 0.71)	0.67 (0.58 to 0.78)
Rifabutin 300 mg once daily	25 mg once daily	18	0.69 (0.62 to 0.76)	0.58 (0.52 to 0.65)	0.52 (0.46 to 0.59)
Rifabutin 300 mg once daily	50 mg once daily	18	1.43 (1.30 to 1.56)	1.16 (1.06 to 1.26)	0.93 (0.85 to 1.01)
			(reference arm for comparison was 25-mg-once-daily rilpivirine administered alone)		
Rifampin 600 mg once daily	150 mg once daily[a]	16	0.31 (0.27 to 0.36)	0.20 (0.18 to 0.23)	0.11 (0.10 to 0.13)
Sildenafil 50 mg single dose	75 mg once daily[a]	16	0.92 (0.85 to 0.99)	0.98 (0.92 to 1.05)	1.04 (0.98 to 1.09)
Simeprevir 150 mg once daily	25 mg once daily	23	1.04 (0.95 to 1.13)	1.12 (1.05 to 1.19)	1.25 (1.16 to 1.35)

n = Maximum number of subjects with data; NA = 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 coadministered drug.

[b] Comparison based on historic controls.

12.4 Microbiology

Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral 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.

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

Antiviral Activity in Cell Culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM to 2.1 nM (0.21 to 0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M [clades A, B, C, D, E, F, and G] and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM.

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). Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M (clades A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 nM to 1.01 nM (0.03 to 0.37 ng/mL) and was less active against group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

Antiviral Activity in Combination with Other Antiviral Agents

Neither dolutegravir nor rilpivirine were antagonistic to all tested anti-HIV agents or with each other when tested in combination.

Resistance

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E, or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

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 frequently observed amino acid substitutions that emerged and conferred decreased phenotypic susceptibility to rilpivirine included: L100I; K101E; V106I and A; V108I; E138K and G, Q, R; V179F and I; Y181C and I; V189I; G190E; H221Y; F227C; and M230I and L.

Virologically Suppressed Subjects: In the pooled SWORD-1 and SWORD-2 trials, 12 subjects (7 in SWORD-1 and 5 in SWORD-2) had confirmed virologic failure (HIV-1 RNA greater than 200 copies/mL) while receiving dolutegravir plus rilpivirine at any time through Week 148. Ten of the confirmed virologic failures had post-baseline resistance data, with 6 isolates showing evidence of rilpivirine resistance, and 2 with evidence of dolutegravir resistance substitutions. Six isolates showed genotypic and/or phenotypic resistance to rilpivirine with emergent NNRTI-resistance substitutions E138E/A (rilpivirine 1.6-fold change), M230M/L (rilpivirine 2-fold change), L100L/I, K101Q and E138A (rilpivirine 4.1-fold change), K101K/E (rilpivirine 1.2-fold change), K101K/E, M230M/L (rilpivirine 2-fold change), and L100L/V/M, M230M/L (rilpivirine 31-fold change). In addition, 1 virologic failure subject had NNRTI-resistance

substitutions K103N and V179I at Week 88 with rilpivirine phenotypic fold change of 5.2 but had no baseline sample.

One virologic failure isolate had emergent INSTI-resistance substitution V151V/I present post-baseline with baseline INSTI-resistance substitutions N155N/H and G163G/R (by exploratory HIV proviral DNA archive sequencing); no integrase phenotypic data were available for this isolate at virologic failure. One other subject had the dolutegravir-resistance substitution G193E at baseline and virologic failure, but no detectable phenotypic resistance (fold change = 1.02) at Week 24.

No resistance-associated substitutions were observed for the 2 subjects meeting confirmed virologic failure in the comparative current antiretroviral regimen arms at Week 48.

Cross-Resistance

Dolutegravir: The susceptibility of dolutegravir was tested against 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).

Rilpivirine: Considering all of the available cell culture and clinical data, any of the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of rilpivirine: K101E or P; E138A, G, K, R, or Q; V179L; Y181C, I, or V; Y188L; H221Y; F227C; M230I or L.

Cross-resistance in site-directed mutant virus has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I, and Y181V conferred 52 times, 15 times, and 12 times decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7 times reduced susceptibility to rilpivirine compared with 2.8 times for E138K alone. The K103N substitution did not show reduced susceptibility to rilpivirine by itself. However, the combination of K103N and L100I resulted in a 7 times reduced susceptibility to rilpivirine. In another study, the Y188L substitution resulted in a reduced susceptibility to rilpivirine of 9 times for clinical isolates and 6 times for site-directed mutants. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to rilpivirine (fold-change range: 3.7 to 554) in 38% and 66% of mutants, respectively.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 20 times higher than those in humans at the recommended dose of 50 mg once daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures approximately 17 times higher than those in humans at the recommended dose of 50 mg once daily.

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 per kg per day were administered to mice and doses of 40, 200, 500, and 1,500 mg per kg per day were administered to rats. In rats, there were no drug-related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21 (mice) and 3 (rats) times higher than those observed in humans at the recommended dose (25 mg once daily).

Mutagenesis

Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

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

Impairment of Fertility

Dolutegravir did not affect male or female fertility in rats at doses associated with exposures approximately 33 times higher than the exposures in humans at the doses of 50 mg once daily.

No human data on the effect of rilpivirine on fertility are available. In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg per kg per day, a dose of rilpivirine 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.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adult Subjects Switching to JULUCA

The efficacy of JULUCA is supported by data from 2 open-label, controlled trials (SWORD-1 [NCT02429791] and SWORD-2 [NCT02422797]) in virologically suppressed patients switching from their current antiretroviral regimen to dolutegravir plus rilpivirine.

SWORD-1 and SWORD-2 are identical 148-week, Phase 3, randomized, multicenter, parallel-group, non-inferiority trials. 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) for at least 6 months (HIV-1 RNA less than 50 copies per mL), with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine received treatment in the trials. Subjects were randomized 1:1 to continue their current antiretroviral regimen (n°=°511) or be switched to dolutegravir plus rilpivirine administered once daily (n°=°513). Subjects originally assigned to continue their current antiretroviral regimen and who remained virologically suppressed at Week 48 switched to dolutegravir plus rilpivirine at Week°52 (n°=°477).

The primary efficacy endpoint for the SWORD trials was the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL at Week 48.

At baseline, in the pooled analysis, the median age of subjects was 43 years (range: 21 to 79), 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 INSTI, respectively, as their baseline third-treatment-agent class prior to randomization. This distribution was similar between treatment arms.

The primary endpoint and other outcomes (including outcomes by key baseline covariates) for the pooled SWORD-1 and SWORD-2 trials are shown in Table 12. The virologic outcome results for SWORD-1 and SWORD-2 were similar to the pooled SWORD-1 and SWORD-2 virologic outcome results.

Table 12. Pooled Virologic Outcomes of Randomized Treatment in SWORD-1 and SWORD-2 Trials at Week 48 in Virologically Suppressed Subjects Who Switched to JULUCA (Snapshot Algorithm)

	Pooled Data	
	Dolutegravir plus Rilpivirine (n = 513)	**Current Antiretroviral Regimen (n = 511)**
HIV-1 RNA <50 copies/mL	95%	95%
Treatment Difference	-0.2% (95% CI: -3.0%, 2.5%)	

HIV-1 RNA ≥50 copies/mL	<1%	1%
Treatment Difference	-0.6 % (95% CI:-1.7%, 0.6%)	
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%
Discontinued due to adverse event or death	3%	<1%
Discontinued for other reasons[a]	1%	3%
Missing data during window but on study	0	<1%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Baseline CD4+ (cells/mm^3)		
<350	88% (n = 58)	88% (n = 52)
≥350	96% (n = 455)	96% (n = 459)
Baseline Third-Treatment-Agent Class		
INSTI	94% (n = 105)	95% (n = 97)
NNRTI	96% (n = 275)	95% (n = 278)
PI	93% (n = 133)	94% (n = 136)
Gender		
Male	95% (n = 393)	96% (n = 403)
Female	93% (n = 120)	91% (n = 108)
Race		
White	94% (n = 421)	95% (n = 400)
African-America/African Heritage/Other	99% (n = 92)	95% (n = 111)
Age (years)		
<50	96% (n = 366)	94% (n = 369)
≥50	93% (n = 147)	96% (n = 142)

INSTI = Integrase strand transfer inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease inhibitor.

[a] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Treatment differences were maintained across baseline characteristics including, CD4+ cell count, age, gender, race, and baseline third-treatment-agent class.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Each JULUCA tablet contains 50 mg of dolutegravir and 25 mg of rilpivirine, and is a pink, oval, film-coated, biconvex tablet debossed with "SV J3T" on one side.

Bottle of 30 tablets with child-resistant closure (contains a desiccant) NDC 49702-242-13.

Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Severe Skin and Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop a rash. Instruct patients to immediately stop taking JULUCA and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as DRESS severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; breathing difficulty; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes; dark or tea-colored urine; pale-colored stools or bowel movements; nausea; vomiting; loss of appetite; or pain, aching, or sensitivity on the right side below the ribs). Advise patients that if hypersensitivity occurs, they will be closely monitored, laboratory tests will be ordered, and appropriate therapy will be initiated *[see Warnings and Precautions (5.1)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with rilpivirine and dolutegravir, components of JULUCA *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatotoxicity is recommended.

Embryo-Fetal Toxicity

Advise individuals of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of JULUCA with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precaution (5.3), Use in Specific Populations (8.1, 8.3)]*.

Individuals of childbearing potential taking JULUCA should be counseled on the consistent use of effective contraception *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

Depressive Disorders

Inform patients that depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with the components of JULUCA. Advise patients to seek immediate medical evaluation if they experience depressive symptoms *[see Warnings and Precautions (5.4), Adverse Reactions (6.1)]*.

Drug Interactions

JULUCA may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.5), Drug Interactions (7)]*.

Administration Instruction

Inform patients that it is important to take JULUCA once daily on a regular dosing schedule with a meal and to avoid missing doses as it can result in development of resistance. Instruct patients that if they miss a dose of JULUCA, to take it as soon as they remember with a meal. Advise patients not to double their next dose. Advise the patient a protein drink alone does not replace a meal *[see Clinical Pharmacology (12.3)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to JULUCA during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Storage

Instruct patients to store JULUCA in the original bottle to protect from moisture and keep the bottle tightly closed. Do not remove desiccant *[see How Supplied/Storage and Handling (16)]*.

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Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

JLC:xPI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

JULUCA (Jah-LOO-kah)

(dolutegravir and rilpivirine tablets)

What is JULUCA?

JULUCA is a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) infection in adults to replace their current anti-HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

It is not known if JULUCA is safe and effective in children.

Do not take JULUCA if you:

- have ever had an allergic reaction to a medicine that contains dolutegravir or rilpivirine.
- are taking any of the following medicines:
  - dofetilide
  - carbamazepine
  - oxcarbazepine
  - phenobarbital
  - phenytoin
  - rifampin
  - rifapentine
  - proton pump inhibitors, including:
    - esomeprazole
    - lansoprazole
    - omeprazole
    - pantoprazole sodium
    - rabeprazole
  - St. John's wort (*Hypericum perforatum*)
  - more than 1 dose of the steroid medicine dexamethasone or dexamethasone sodium phosphate

Before you take JULUCA, tell your healthcare provider about all of your medical conditions, including if you:

- have ever had a severe skin rash or an allergic reaction to medicines that contain dolutegravir or rilpivirine.
- have or have had liver problems, including hepatitis B or C infection.
- have ever had a mental health problem.
- are pregnant or plan to become pregnant. One of the medicines in JULUCA called dolutegravir may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than JULUCA if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy.
  - If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with JULUCA.
  - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with JULUCA.

- Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with JULUCA.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including JULUCA, during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take JULUCA.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - One of the medicines in JULUCA (dolutegravir) passes to your baby in your breast milk.

  Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with JULUCA. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with JULUCA.
- Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take JULUCA with other medicines.

How should I take JULUCA?

- **Take JULUCA 1 time a day exactly as your healthcare provider tells you.**
- **Always take JULUCA with a meal.** A protein drink alone does not replace a meal.
- Do not change your dose or stop taking JULUCA without talking with your healthcare provider.
- If you take an H_2-receptor antagonist (famotidine, cimetidine, nizatidine, or ranitidine), JULUCA should be taken at least 4 hours before or 12 hours after you take these medicines.
- If you take antacids, laxatives, or other products that contain aluminum, calcium carbonate, magnesium, or buffered medicines, JULUCA should be taken at least 4 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with JULUCA:
  - You may take these supplements at the same time that you take JULUCA with food.
  - If you do not take these supplements with JULUCA and food, take JULUCA at least 4 hours before or 6 hours after you take these supplements.
- Do not miss a dose of JULUCA.
- If you miss a dose of JULUCA, take it as soon as you remember with a meal. Do not take 2 doses at the same time.
- Stay under the care of a healthcare provider during treatment with JULUCA.
- Do not run out of JULUCA. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much JULUCA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of JULUCA?

JULUCA can cause serious side effects, including:

Severe skin rash and allergic reactions. Call your healthcare provider right away if you develop a rash with JULUCA**. Stop taking JULUCA and get medical help right away if you develop a rash with any of the following signs or symptoms:**

- fever
- generally ill feeling
- tiredness
- muscle or joint aches
- blisters or sores in mouth
- blisters or peeling of the skin
- redness or swelling of the eyes
- swelling of the mouth, face, lips, or tongue
- problems breathing

- **Liver problems**. People with a history of hepatitis B or C virus who have certain liver function test changes may have an increased risk of developing new or worsening changes in certain liver tests during treatment with JULUCA. Liver problems, including liver failure, have also happened in people without history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver function. **Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area
- **Depression or mood changes. Tell your healthcare provider right away or get medical help if you have any of the following symptoms:**
  - feeling sad or hopeless
  - feeling anxious or restless
  - have thoughts of hurting yourself (suicide) or have tried to hurt yourself
- **The most common side effects of JULUCA include:**
  - diarrhea
  - nausea
  - headache

These are not all the possible side effects of JULUCA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JULUCA?

- Store JULUCA at room temperature between 68°F to 77°F (20°C to 25°C).
- Store JULUCA tablets in the original bottle. Keep the bottle tightly closed and protected from moisture.
- The bottle of JULUCA contains a desiccant to help keep your medicine dry (protect it from moisture). Keep the desiccant in the bottle. Do not remove the desiccant.

Keep JULUCA and all medicines out of the reach of children.

General information about the safe and effective use of JULUCA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use JULUCA for a condition for which it was not prescribed. Do not give JULUCA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about JULUCA that is written for health professionals.

What are the ingredients in JULUCA?

Active ingredients: dolutegravir and rilpivirine.

Inactive ingredients: croscarmellose sodium, D-mannitol, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, povidone K29/32 and K30, silicified microcrystalline cellulose, sodium starch glycolate, and sodium stearyl fumarate.

The tablet film-coating contains: iron oxide red, iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

Manufactured for:

ViiV Healthcare

Durham, NC 27701

by:

GlaxoSmithKline

Durham, NC 27701

JLC:xPIL

For more information go to www.JULUCA.com or call 1-877-844-8872.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised:10/2022

Proposed Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JULUCA safely and effectively. See full prescribing information for JULUCA.

JULUCA (dolutegravir and rilpivirine tablets), for oral use
Initial U.S. Approval: 2017

---------- INDICATIONS AND USAGE----------
JULUCA, a two-drug combination of dolutegravir, an HIV-1 integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those 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 treatment failure and no known substitutions associated with resistance to the individual components of JULUCA. (1)

----------DOSAGE AND ADMINISTRATION ----------
- Pregnancy Testing: Pregnancy testing is recommended before initiation of JULUCA in individuals of childbearing potential. (2.1, 5.3, 8.1, 8.3)
- One tablet taken orally once daily with a meal. (2.2)
- Rifabutin coadministration: Take an additional 25-mg tablet of rilpivirine with JULUCA once daily with a meal for the duration of the rifabutin coadministration. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
Each tablet contains: 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride). (3)

---------- CONTRAINDICATIONS ----------
- Previous hypersensitivity reaction to dolutegravir or rilpivirine. (4)
- Coadministration with dofetilide. (4)
- Coadministration with drugs where significant decreases in rilpivirine plasma concentrations may occur, which may result in loss of virologic response. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Severe skin and hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported with the individual components. Discontinue JULUCA immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)
- Hepatotoxicity has been reported in patients receiving a dolutegravir- or rilpivirine-containing regimen. Monitoring for hepatotoxicity is recommended. (5.2)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of JULUCA and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Individuals of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.3, 8.1, 8.3)
- Depressive disorders have been reported with the use of rilpivirine- or dolutegravir-containing regimens. Immediate medical evaluation is recommended for severe depressive symptoms. (5.4, 6.1)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (all grades) observed in at least 2% of subjects were diarrhea, headache, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
- Because JULUCA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Refer to the full prescribing information for important drug interactions with JULUCA. (4, 5.4, 7)
- Drugs that induce or inhibit cytochrome P450 (CYP)3A4 or uridine diphosphate glucuronosyltransferase (UGT)1A1 may affect the plasma concentrations of the components of JULUCA. (7.3)
- Drugs that increase gastric pH or containing polyvalent cations may decrease plasma concentrations of the components of JULUCA. (4, 7.3, 7.4)
- Consider alternatives to prescribing JULUCA with drugs with a known risk of Torsade de Pointes. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Assess the risks and benefits of JULUCA and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1, 8.3)
- Rilpivirine exposure during pregnancy: Total rilpivirine exposures were generally lower during pregnancy compared with the postpartum period. (8.1, 12.3).
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in individuals of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

JULUCA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those 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 treatment failure and no known substitutions associated with resistance to the individual components of JULUCA.

2 DOSAGE AND ADMINISTRATION

2.1 Pregnancy Testing before Initiation of JULUCA

Pregnancy testing is recommended before initiation of JULUCA in individuals of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage

The recommended dosage of JULUCA is one tablet taken orally once daily with a meal *[see Clinical Pharmacology (12.3)]*. One tablet of JULUCA contains 50 mg of dolutegravir and 25 mg of rilpivirine.

2.3 Recommended Dosage with Rifabutin Coadministration

If JULUCA is coadministered with rifabutin, take an additional 25-mg tablet of rilpivirine with JULUCA once daily with a meal for the duration of the rifabutin coadministration *[see Drug Interactions (7.4)]*.

3 DOSAGE FORMS AND STRENGTHS

JULUCA tablets are pink, oval, biconvex tablets debossed with “SV J3T” on one side. Each film-coated tablet contains 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride).

4 CONTRAINDICATIONS

JULUCA is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir or rilpivirine *[see Warnings and Precautions (5.1)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7)]*.
- receiving other coadministered drugs in Table 1 that significantly decrease rilpivirine plasma concentrations *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Table 1. Drugs That are Contraindicated with JULUCA

Drug Class	Contraindicated Drugs in Class	Clinical Comment
Antiarrhythmic	Dofetilide	Potential for serious and/or life-threatening events due to the potential for increased dofetilide plasma concentrations.
Anticonvulsants	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Potential for significant decreases in rilpivirine plasma concentrations due to cytochrome P450 (CYP)3A enzyme induction, which may result in loss of virologic response.
Antimycobacterials	Rifampin Rifapentine	
Glucocorticoid (systemic)	Dexamethasone (more than a single-dose treatment)	
Herbal Products	St John's wort (*Hypericum perforatum*)	
Proton Pump Inhibitors	e.g., Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	Potential for significant decreases in rilpivirine plasma concentrations due to gastric pH increase, which may result in loss of virologic response.

5 WARNINGS AND PRECAUTIONS

5.1 Skin and Hypersensitivity Reactions

Hypersensitivity reactions have been reported with dolutegravir and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. These events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials.

Severe skin and hypersensitivity reactions have been reported during postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. 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 subjects. No Grade 4 rash was reported *[see Adverse Reactions (6.2)]*.

Discontinue JULUCA 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 after the onset of hypersensitivity may result in a life-threatening reaction *[see Contraindications (4)]*.

5.2 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir- or rilpivirine-containing regimen *[see Adverse Reactions (6.1)]*. 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.

5.3 Embryo-Fetal Toxicity

An ongoing observational study showed 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. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform individuals of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with JULUCA. Assess the risks and benefits of JULUCA and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester *[see Use in Specific Populations (8.1. 8.3)]*.

Pregnancy testing is recommended before initiation of JULUCA in individuals of childbearing potential *[see Dosage and Administration (2.1)]*.

Individuals of childbearing potential should be counseled on the consistent use of effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

JULUCA may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.4 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 *[see Adverse Reactions (6.1)]*. For information regarding depressive disorders reported in patients taking dolutegravir, *see Adverse Reactions (6.1)*. 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.

5.5 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 (4), Drug Interactions (7.4)]:*

- 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 of 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 Drug Interactions (7.3), Clinical Pharmacology (12.2)]*. 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.

6 ADVERSE REACTIONS

The following adverse reactions are described below and in other sections of the labeling:

- Skin and hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*.
- Depressive disorders *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of JULUCA is based on the pooled primary Week 48 analyses of data from 2 identical, international, multicenter, open-label trials, SWORD-1 and SWORD-2, including additional follow up through Week 148.

A total of 1,024 adult HIV-1–infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 nucleoside reverse transcriptase inhibitors [NRTIs] plus either an integrase strand transfer inhibitor [INSTI], a non-nucleoside reverse transcriptase inhibitor [NNRTI], or a protease inhibitor [PI]) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine, were randomized and received treatment. Subjects were randomized 1:1 to continue their current antiretroviral regimen or be switched to dolutegravir plus rilpivirine administered once daily. Subjects originally assigned to continue their current antiretroviral regimen and who remained virologically suppressed at Week 48 switched to dolutegravir plus rilpivirine at Week 52. In the pooled analyses, the proportion of subjects who discontinued treatment due to an adverse event through Week 48 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 through Week 48 were psychiatric disorders: 2% of subjects receiving dolutegravir plus rilpivirine and less than 1% on the current antiretroviral regimen. In the pooled analyses, the proportion of subjects receiving dolutegravir plus rilpivirine who discontinued treatment due to an adverse event through Week 148 was 8%.

The most common adverse reactions (ARs) (all grades) reported in at least 2% of subjects in the Week 48 pooled analyses from SWORD-1 and SWORD-2 are provided in Table 2.

Table 2. Adverse Reactions (Grades 1 to 4) Reported in at Least 2% of Virologically Suppressed Subjects with HIV-1 Infection in SWORD-1 and SWORD-2 Trials (Week 48 Pooled Analyses)

Adverse Reaction	Dolutegravir plus Rilpivirine (n = 513)	Current Antiretroviral Regimen (n = 511)
Diarrhea	2%	<1%
Headache	2%	0

In the Week 148 pooled analyses, the only adverse reaction (all grades) occurring in at least 2% of subjects who received dolutegravir plus rilpivirine and that was not observed during the Week 48 analyses was nausea (2%).

Less Common Adverse Reactions

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

General Disorders: Fatigue.

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

Hepatobiliary Disorders: Cholecystitis, cholelithiasis, hepatitis.

Immune System Disorders: Immune reconstitution syndrome.

Metabolism and Nutrition Disorders: Decreased appetite.

Musculoskeletal Disorders: Myositis.

Nervous System Disorders: Dizziness, somnolence.

Psychiatric Disorders: Depressive disorders including depressed mood; depression; suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness. Other reported psychiatric adverse reactions include anxiety, insomnia, sleep disorders, and abnormal dreams.

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

Skin and Subcutaneous Tissue Disorders: Pruritus, rash.

Laboratory Abnormalities

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in the Week 48 pooled analysis are presented in Table 3.

Table 3. Selected Laboratory Abnormalities (Grades 2 and 3 to 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) Grade 3 to 4 (≥10.0 x ULN)	 <1% 1%	 <1% 2%
Hyperglycemia Grade 2 (126-250 mg/dL) Grade 3 to 4 (>250 mg/dL)	 4% <1%	 5% <1%
Lipase Grade 2 (>1.5-3.0 x ULN) Grade 3 to 4 (>3.0 x ULN)	 5% 2%	 5% 2%

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal.

In the Week 148 pooled analyses, there were no additional selected laboratory abnormalities with dolutegravir plus rilpivirine compared with those shown in Table 3.

Changes in Serum Creatinine: Dolutegravir and rilpivirine have been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment with dolutegravir plus rilpivirine and remained stable through 148 weeks. Mean changes from baseline of 0.093 mg per dL (range: -0.30 to 0.58 mg per dL) and 0.112 mg per dL (range: -0.24 to 0.81 mg per dL) were observed after 48 and 148°weeks of treatment with dolutegravir plus rilpivirine, respectively. These changes are not considered to be clinically relevant.

Serum Lipids: At 48 weeks, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol to HDL ratio were similar between the treatment arms, with no further notable changes beyond Week 48.

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) 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. In subjects who received dolutegravir plus rilpivirine from study start and were continuing JULUCA at Week 148, mean BMD increases from baseline were 0.98% (total hip) and 0.53% (lumbar spine). 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving a dolutegravir- or rilpivirine-containing regimen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Investigations

Weight increased.

Musculoskeletal Disorders

Arthralgia, myalgia.

Renal and Genitourinary Disorders

Nephrotic syndrome.

Skin and Subcutaneous Tissue Disorders

Severe skin and hypersensitivity reactions, including DRESS.

7 DRUG INTERACTIONS

7.1 Concomitant Use with Other Antiretroviral Medicines

Because JULUCA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended *[see Indications and Usage (1)]*. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided *[see Contraindications (4), Warnings and Precautions (5.5), Clinical Pharmacology (12.3)]*.

7.2 Potential for JULUCA to Affect Other Drugs

Dolutegravir, a component of JULUCA, inhibits the renal organic cation transporters (OCT)2 and multidrug and toxin extrusion transporter (MATE)1, thus it may increase plasma

concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide, dalfampridine, and metformin *[see Contraindications (4), Drug Interactions (7.4)]*.

7.3 Potential for Other Drugs to Affect the Components of JULUCA

Dolutegravir

Dolutegravir is metabolized by uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 with some contribution from cytochrome P450 (CYP)3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir *[see Drug Interactions (7.4)]*. Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

Coadministration of dolutegravir with polyvalent cation-containing products may lead to decreased absorption of dolutegravir *[see Drug Interactions (7.4)]*.

Rilpivirine

Rilpivirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of rilpivirine. Coadministration of JULUCA and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs *[see Contraindications (4), Drug Interactions (7.4)]*. Coadministration of JULUCA and drugs 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 *[see Contraindications (4), Drug Interactions (7.4), Clinical Pharmacology (12.3)]*.

QT-Prolonging Drugs: In healthy subjects, 75 mg once daily of 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 Clinical Pharmacology (12.2)]*. Consider alternatives to JULUCA when coadministered with a drug with a known risk of Torsade de Pointes.

7.4 Established and Other Potentially Significant Drug Interactions

Information regarding potential drug interactions with dolutegravir and rilpivirine are provided in Table 4. These recommendations are based on either drug interaction trials of individual components or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy *[see Contraindications (4), Warnings and Precautions (5.5), Clinical Pharmacology (12.3)]*.

Table 4. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions[a]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antacids (e.g., aluminum or magnesium hydroxide, calcium carbonate)	↓Rilpivirine	Administer JULUCA 4 hours before or 6 hours after taking antacids.
Antiarrhythmic: Dofetilide	↑Dofetilide	Coadministration is contraindicated with JULUCA *[see Contraindications (4)]*.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓Dolutegravir ↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.
Antidiabetic: Metformin[b]	↑Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use of JULUCA and metformin.
Antimycobacterials: Rifampin Rifapentine	↓Dolutegravir ↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.
Antimycobacterial: Rifabutin[b]	↔Dolutegravir ↔Rifabutin ↓Rilpivirine	An additional rilpivirine 25-mg tablet should be taken with JULUCA once daily with a meal when rifabutin is coadministered.
Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment)	↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.
H_2-receptor antagonists: Famotidine Cimetidine Nizatidine Ranitidine	↔Dolutegravir ↓Rilpivirine	JULUCA should only be administered at least 4 hours before or 12 hours after taking H_2-receptor antagonists.

Herbal product: St John's wort (*Hypericum perforatum*)	↓ Dolutegravir ↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.
Macrolide or ketolide antibiotics: Clarithromycin Erythromycin Telithromycin	↔Dolutegravir ↑Rilpivirine	Where possible, consider alternatives, such as azithromycin.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing products[b] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer JULUCA 4 hours before or 6 hours after taking products containing polyvalent cations.
Narcotic analgesic: Methadone[b]	↔Dolutegravir ↓Methadone ↔Rilpivirine	No dose adjustments are required when starting coadministration of methadone with JULUCA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Oral calcium and iron supplements, including multivitamins containing calcium or iron[b] (non-antacid)	↓Dolutegravir	Administer JULUCA and supplements containing calcium or iron together with a meal or take JULUCA 4 hours before or 6 hours after taking these supplements.
Potassium channel blocker: Dalfampridine	↑Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with JULUCA should be considered against the risk of seizures in these patients.
Proton pump inhibitors: e.g., Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	↓Rilpivirine	Coadministration is contraindicated with JULUCA due to decreased rilpivirine concentrations *[see Contraindications (4)]*.

↑ = Increase, ↓ = Decrease, ↔ = No change.

[a] This table is not all inclusive.
[b] *See Clinical Pharmacology (12.3) for magnitude of interaction.*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to JULUCA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Data from an ongoing birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir, a component of JULUCA, is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise individuals of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with use of JULUCA. Assess the risks and benefits of JULUCA and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development *[see Warnings and Precaution (5.3)]*.

There are insufficient human data on the use of JULUCA during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. 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 recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of JULUCA at systemic exposures (AUC) to dolutegravir less than (rabbits) and 38 times (rats) and exposures to rilpivirine 15 (rats) and 70 (rabbits) times the exposure at the recommended human dose (RHD) of JULUCA *(see Data)*.

Data

Human Data: Dolutegravir: In a birth outcome surveillance study in Botswana, there were 7 cases of neural tube defects reported out of 3,591 deliveries (0.19%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural

tube defect prevalence rates were 0.11% (21/19,361 deliveries) in the non-dolutegravir arm and 0.07% (87/119,630 deliveries) in the HIV-uninfected arm. Seven cases reported with dolutegravir included 3 cases of myelomeningocele, 2 cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, no increased risk of neural tube defects was identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 5 infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy. The reported risks of neural tube defects by treatment groups were based on interim analyses from the ongoing surveillance study in Botswana. It is unknown if baseline characteristics were balanced between the study treatment groups. The observed trends of association could change as data accumulate.

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to definitively address the risk of neural tube defects with dolutegravir.

Data from the birth outcome surveillance study described above and postmarketing sources with more than 1,000 pregnancy outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) following second-/third-trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

Dolutegravir has been shown to cross the placenta. In a clinical trial in Uganda and South Africa in women during the last trimester of pregnancy receiving dolutegravir 50 mg once daily, the ratio of median dolutegravir concentration in fetal umbilical cord to that in maternal peripheral plasma was 1.21 (range 0.51-2.11) (n = 15).

Rilpivirine: Based on prospective reports to the APR of over 610 exposures to rilpivirine-containing regimens during pregnancy resulting in live births (including over 420 exposed during the first trimester and over 190 exposed in the second/third trimester), there was no significant difference between the overall risk of birth defects for rilpivirine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 1.4% (95% CI: 0.5% to 3.0%) and 1.6% (95% CI: 0.3% to 4.5%) following first and second/third trimester exposure, respectively, to rilpivirine-containing regimens.

Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 HIV-1–infected pregnant subjects during the second and third trimesters and postpartum. Each of the subjects were on a rilpivirine-based regimen at the time of enrollment. Twelve subjects

completed the trial through the postpartum period (6 to 12 weeks after delivery) and pregnancy outcomes are missing for 6 subjects. The exposure (C_{0h} and AUC) of total rilpivirine was approximately 30% to 40% lower during pregnancy compared with postpartum (6 to 12 weeks). The protein binding of rilpivirine was similar (>99%) during the second trimester, third trimester, and the postpartum period *[see Clinical Pharmacology (12.3)]*. One subject discontinued the trial following fetal death at 25 weeks' gestation due to suspected premature rupture of membranes. Among the 12 subjects who were virologically suppressed at baseline (less than 50 copies/mL), virologic response was preserved in 10 subjects (83.3%) through the third trimester visit and in 9 subjects (75%) through the 6- to 12-week postpartum visit. Virologic outcomes during the third trimester visit were missing for 2 subjects who were withdrawn (one subject was nonadherent to the study drug and one subject withdrew consent). Among the 10 infants with HIV test results available, born to 10 HIV-1–infected pregnant subjects, all had negative test results for HIV-1 at the time of delivery and up to 16 weeks postpartum. All 10 infants received antiretroviral prophylactic treatment with zidovudine. 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.

Animal Data: Dolutegravir: Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on Gestation Days 6 to 17 and 6 to 18, respectively, and to rats on Gestation Day 6 to Lactation/Post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans, and in rats were approximately 38 times the exposure in humans (50 mg once daily). In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 32 times the human exposure with 50 mg once daily).

Rilpivirine: Rilpivirine was administered orally to pregnant rats (40, 120, or 400 mg per kg per day) and rabbits (5, 10, or 20 mg per kg per day) through organogenesis (on Gestation Days 6 through 17, and 6 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with rilpivirine in rats and rabbits at exposures 15 (rats) and 70 (rabbits) times higher than the exposure in humans at the recommended dose of 25 mg once daily. In a pre/postnatal development study with rilpivirine, where rats were administered up to 400 mg per kg per day through lactation, no significant adverse effects directly related to drug were noted in the offspring.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Dolutegravir is present in human milk. It is not known whether JULUCA or components of JULUCA affect human milk production or have effects on the breastfed infant. When administered to lactating rats, rilpivirine was present in milk *(see Data)*.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving JULUCA.

Data

Animal Data: Rilpivirine: In animals, no studies have been conducted to assess the excretion of rilpivirine into milk directly; however, rilpivirine was present in plasma of rat pups exposed through the milk of lactating rats (dosed up to 400 mg per kg per day).

8.3 Females and Males of Reproductive Potential

In individuals of childbearing potential currently on JULUCA who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing JULUCA and discuss with the patient if an alternative treatment should be considered *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended in individuals of childbearing potential before initiation of JULUCA *[see Dosage and Administration (2.1)]*.

Contraception

Individuals of childbearing potential who are taking JULUCA should be counseled on the consistent use of effective contraception.

8.4 Pediatric Use

The safety and efficacy of JULUCA have not been established in pediatric patients.

8.5 Geriatric Use

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 *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dosage adjustment is necessary for patients with mild or moderate renal impairment (creatinine clearance greater than or equal to 30 mL/min) *[see Clinical Pharmacology (12.3)]*. In patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease, increased monitoring for adverse effects is recommended.

8.7 Hepatic Impairment

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir or rilpivirine is unknown *[see Clinical Pharmacology (12.3)]*.

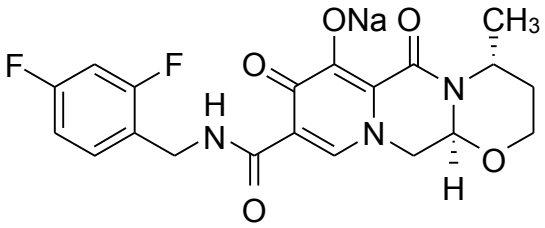
10 OVERDOSAGE

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 and ECG (QT interval) as well as observation of the clinical status of the patient. As both dolutegravir and rilpivirine are highly bound to plasma proteins, it is unlikely that either would be significantly removed by dialysis.

11 DESCRIPTION

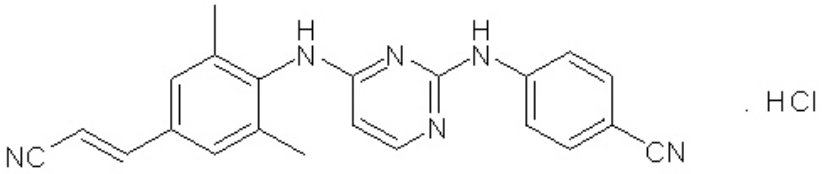
JULUCA is a fixed-dose combination tablet containing dolutegravir (as dolutegravir sodium), an INSTI, and rilpivirine (as rilpivirine hydrochloride), an NNRTI.

The chemical name of dolutegravir sodium is 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. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol. It has the following structural formula:



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

The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6 \cdot HCl$ and its molecular weight is 402.88g per mol. Rilpivirine hydrochloride has the following structural formula:



Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

JULUCA tablets are for oral administration. Each film-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride) and the inactive ingredients croscarmellose sodium, D-mannitol, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, povidone K29/32 and K30, silicified microcrystalline cellulose, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients iron oxide red, iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

JULUCA is a fixed-dose combination of the HIV-1 antiretroviral agents, dolutegravir and rilpivirine *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of JULUCA on the QT interval has not been studied.

In a randomized, placebo-controlled, crossover trial, 42 healthy subjects received single-dose oral administration 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. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours postdose.

The effect of rilpivirine at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo- and active- (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady state. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction was 2.0 (5.0) milliseconds (i.e., below the threshold of clinical concern). When 75 mg and 300 mg once daily of rilpivirine (3 times and 12 times the recommended dosage in JULUCA, respectively) 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) milliseconds, respectively. Steady-state administration of rilpivirine 75 mg once daily and 300 mg once daily resulted in a mean steady-state C_{max} approximately 2.6-fold and 6.7-fold, respectively, higher than the mean C_{max} observed with the recommended 25-mg once-daily dose of rilpivirine *[see Drug Interactions (7.4)]*.

Effects on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg

once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of JULUCA are provided in Table 5. The multiple-dose pharmacokinetic parameters are provided in Table 6.

Table 5. Pharmacokinetic Properties of the Components of JULUCA

	Dolutegravir	**Rilpivirine**
Absorption		
T_{max} (h)	3	4
Effect of moderate-fat meal (relative to fasting)[a]	AUC Ratio 1.87 (1.54, 2.26)	AUC Ratio 1.57 (1.24, 1.98)
Effect of high-fat meal (relative to fasting)[a]	AUC Ratio 1.87 (1.53, 2.29)	AUC Ratio 1.72 (1.36, 2.16)
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)	14	50
% of dose excreted as total ^{14}C (unchanged drug) in urine[b]	31 (<1)	6.5 (<1)
% of dose excreted as total ^{14}C (unchanged drug) in feces[b]	64 (53)	85 (25)

UGT = uridine diphosphate glucuronosyltransferase; CYP = Cytochrome P450.

[a] Geometric mean ratio (fed/fasted) in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~900 kcal, 56% fat. Moderate-fat meal = ~625 kcal, 32% fat. When rilpivirine was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal.

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

Table 6. Multiple-Dose Pharmacokinetic Properties of the Components of JULUCA

Parameter Mean (CV%)	Dolutegravir[a]	Rilpivirine[a]
C_{max} (mcg/mL)	3.67 (20)	0.13 (54)[b]
AUC_{tau} (mcg/h/mL)	53.6 (27)	2.2 (38)
C_{trough} (mcg/mL)	1.11 (46)	0.08 (44)

[a] Based on population pharmacokinetic analyses using pooled data from ART treatment-naïve adults receiving 50 mg dolutegravir once daily or 25 mg rilpivirine once daily.

[b] Observed C_{max} in a pharmacokinetic substudy in ART treatment-naïve adults receiving 25 mg rilpivirine once daily.

Specific Populations

Pediatric Patients: The pharmacokinetics of dolutegravir plus rilpivirine has not been studied in pediatric subjects *[see Use in Specific Populations (8.4)]*.

Geriatric Patients: Population pharmacokinetic analyses from studies with the individual components indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir or rilpivirine. Pharmacokinetic data in subjects 65 years of age and older are limited *[see Use in Specific Populations (8.5)]*.

Patients with Renal Impairment: Population pharmacokinetic analyses indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. Dolutegravir AUC, C_{max}, and C_{24} 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. There is inadequate information to recommend appropriate dosing of dolutegravir in patients requiring dialysis *[see Use in Specific Populations (8.6)]*.

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.

Patients with Hepatic Impairment: Dolutegravir exposures were similar in subjects (n = 8) with moderate hepatic impairment (Child-Pugh Score B) as compared with matched healthy controls. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

Rilpivirine exposure was 47% higher in subjects (n = 8) with mild hepatic impairment (Child-Pugh Score A) and 5% higher in subjects (n = 8) with moderate hepatic impairment (Child-Pugh Score B) compared with matched controls. The effect of severe hepatic impairment (Child-Pugh

Score C) on the pharmacokinetics of rilpivirine has not been studied *[see Use in Specific Populations (8.7)]*.

Patients with HBV/HCV Co-infection: Population pharmacokinetic analyses indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure of dolutegravir or rilpivirine. Subjects with hepatitis B co-infection were excluded from studies with dolutegravir plus rilpivirine.

Gender and Race: Population pharmacokinetic analyses from studies with the individual components revealed that gender and race had no clinically relevant effect on the pharmacokinetics of dolutegravir or rilpivirine.

Pregnancy and Postpartum: Rilpivirine: The exposure (C_{0h} and AUC_{24h}) to total rilpivirine after taking rilpivirine 25 mg once daily as part of an antiretroviral regimen was 30% to 40% lower during pregnancy (similar for the second and third trimesters) compared with postpartum (see Table 7). However, the exposure during pregnancy was not significantly different from exposures obtained in Phase 3 trials of rilpivirine-containing regimens. Based on the exposure-response relationship for rilpivirine, this decrease is not considered clinically relevant in patients who are virologically suppressed. The protein binding of rilpivirine was similar (>99%) during the second trimester, third trimester, and postpartum.

Table 7. Pharmacokinetic Results of Rilpivirine during the 2nd and 3rd Trimesters of Pregnancy and Postpartum Period[a]

Pharmacokinetics of Total Rilpivirine (mean ± SD)	Postpartum (6 to 12 Weeks) (n = 11)	2nd Trimester of Pregnancy (n = 15)	3rd Trimester of Pregnancy (n = 13)
C_{0h} (ng/mL)	111 ± 69.2	65.0 ± 23.9	63.5 ± 26.2
C_{min} (ng/mL)	84.0 ± 58.8	54.3 ± 25.8	52.9 ± 24.4
C_{max} (ng/mL)	167 ± 101	121 ±45.9	123 ± 47.5
T_{max} (h), median (range)	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC_{24h} (ng.h/mL)	2,714 ± 1,535	1,792 ± 711	1,762 ± 662

[a] Total rilpivirine exposure after administration of rilpivirine 25 mg once daily as part of an antiretroviral regimen.

Drug Interaction Studies

Drug interaction trials were conducted with dolutegravir or rilpivirine as individual components and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-gp, BCRP, bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

In vitro, dolutegravir inhibited the renal OCT2 (IC_{50} = 1.93 microM) and MATE1 (IC_{50} = 6.34 microM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide, dalfampridine, and metformin *[see Contraindications (4), Drug Interactions (7.4)]*.

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT)1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

Rilpivirine is primarily metabolized by CYP3A. Rilpivirine 25 mg once daily is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes.

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir or rilpivirine are provided in Table 4 *[see Drug Interactions (7.4)]*.

Table 8. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir**	**n**	**Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00**		
			C_{max}	**AUC**	**C_τ or C_{24}**
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79 to 1.15)	_
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)

[a] The number of subjects represents the maximum number of subjects that were evaluated.

Table 9. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)

Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[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.

[c] The number of subjects represents the maximum number of subjects that were evaluated.

Table 10. Summary of Effect of Rilpivirine on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	**Dose of Rilpivirine**	**n**	**Geometric Mean Ratio (90% CI) of Coadministered Drug Pharmacokinetic Parameters with/without EDURANT No Effect = 1.00**		
			C_{max}	**AUC**	**C_{min}**
Acetaminophen 500 mg single dose	150 mg once daily[a]	16	0.97 (0.86 to 1.10)	0.91 (0.86 to 0.97)	NA
Atorvastatin 40 mg once daily 2-hydroxy-atorvastatin 4-hydroxy-atorvastatin	150 mg once daily[a]	16	1.35 (1.08 to 1.68) 1.58 (1.33 to 1.87) 1.28 (1.15 to 1.43)	1.04 (0.97 to 1.12) 1.39 (1.29 to 1.50) 1.23 (1.13 to 1.33)	0.85 (0.69 to 1.03) 1.32 (1.10 to 1.58) NA
Chlorzoxazone 500 mg single dose taken 2 hours after rilpivirine	150 mg once daily[a]	16	0.98 (0.85 to 1.13)	1.03 (0.95 to 1.13)	NA
Digoxin 0.5 mg single dose	25 mg once daily	22	1.06 (0.97 to 1.17)	0.98 (0.93 to 1.04)[c]	NA
Ethinylestradiol 0.035 mg once daily Norethindrone 1 mg once daily	25 mg once daily	17	1.17 (1.06 to 1.30) 0.94 (0.83 to 1.06)	1.14 (1.10 to 1.19) 0.89 (0.84 to 0.94)	1.09 (1.03 to 1.16) 0.99 (0.90 to 1.08)
Ketoconazole 400 mg once daily	150 mg once daily[a]	14	0.85 (0.80 to 0.90)	0.76 (0.70 to 0.82)	0.34 (0.25 to 0.46)
Methadone 60-100 mg once daily, individualized dose R(-) methadone	25 mg once daily	13	0.86 (0.78 to 0.95)	0.84 (0.74 to 0.95)	0.78 (0.67 to 0.91)

S(+) methadone			0.87 (0.78 to 0.97)	0.84 (0.74 to 0.96)	0.79 (0.67 to 0.92)
Metformin 850 mg single dose	25 mg once daily	20	1.02 (0.95 to -1.10)	0.97 (0.90 to 1.06)[b]	NA
Omeprazole 20 mg once daily	150 mg once daily[a]	15	0.86 (0.68 to 1.09)	0.86 (0.76 to 0.97)	NA
Rifampin 600 mg once daily 25-desacetylrifampin	150 mg once daily[a]	16	1.02 (0.93 to 1.12) 1.00 (0.87 to 1.15)	0.99 (0.92 to 1.07) 0.91 (0.77 to 1.07)	NA NA
Sildenafil 50 mg single dose *N*-desmethyl-sildenafil	75 mg once daily[a]	16	0.93 (0.80 to 1.08) 0.90 (0.80 to 1.02)	0.97 (0.87 to 1.08) 0.92 (0.85 to 0.99)[c]	NA NA
Simeprevir 150 mg once daily	25 mg once daily	21	1.10 (0.97 to 1.26)	1.06 (0.94 to 1.19)	0.96 (0.83 to 1.11)

n = Maximum number of subjects 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 coadministered drug.

[b] N (maximum number of subjects with data) for $AUC_{(0-\infty)}$ = 15.

[c] $AUC_{(0\text{-last})}$.

Table 11. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Rilpivirine

Coadministered Drug(s) and Dose(s)	**Dose of Rilpivirine**	**n**	**Geometric Mean Ratio (90% CI) of Rilpivirine Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00**		
			C_{max}	**AUC**	**C_{min}**
Acetaminophen 500 mg single dose	150 mg once daily[a]	16	1.09 (1.01 to 1.18)	1.16 (1.10 to 1.22)	1.26 (1.16 to 1.38)
Atorvastatin 40 mg once daily	150 mg once daily[a]	16	0.91 (0.79 to 1.06)	0.90 (0.81 to 0.99)	0.90 (0.84 to 0.96)
Chlorzoxazone 500 mg single dose taken 2 hours after rilpivirine	150 mg once daily[a]	16	1.17 (1.08 to 1.27)	1.25 (1.16 to 1.35)	1.18 (1.09 to 1.28)
Ethinylestradiol/ Norethindrone 0.035 mg once daily/ 1 mg once daily	25 mg once daily	15	↔[b]	↔[b]	↔[b]
Famotidine 40 mg single dose taken 12 hours before rilpivirine	150 mg single dose[a]	24	0.99 (0.84 to 1.16)	0.91 (0.78 to 1.07)	NA

Famotidine 40 mg single dose taken 2 hours before rilpivirine	150 mg single dose[a]	23	0.15 (0.12 to 0.19)	0.24 (0.20 to 0.28)	NA
Famotidine 40 mg single dose taken 4 hours after rilpivirine	150 mg single dose[a]	24	1.21 (1.06 to 1.39)	1.13 (1.01 to 1.27)	NA
Ketoconazole 400 mg once daily	150 mg once daily[b]	15	1.30 (1.13 to 1.48)	1.49 (1.31 to 1.70)	1.76 (1.57 to 1.97)
Methadone 60-100 mg once daily, individualized dose	25 mg once daily	12	↔[b]	↔[b]	↔[b]
Omeprazole 20 mg once daily	150 mg once daily[a]	16	0.60 (0.48 to 0.73)	0.60 (0.51 to 0.71)	0.67 (0.58 to 0.78)
Rifabutin 300 mg once daily	25 mg once daily	18	0.69 (0.62 to 0.76)	0.58 (0.52 to 0.65)	0.52 (0.46 to 0.59)
Rifabutin 300 mg once daily	50 mg once daily	18	1.43 (1.30 to 1.56)	1.16 (1.06 to 1.26)	0.93 (0.85 to 1.01)
			(reference arm for comparison was 25-mg-once-daily rilpivirine administered alone)		
Rifampin 600 mg once daily	150 mg once daily[a]	16	0.31 (0.27 to 0.36)	0.20 (0.18 to 0.23)	0.11 (0.10 to 0.13)
Sildenafil 50 mg single dose	75 mg once daily[a]	16	0.92 (0.85 to 0.99)	0.98 (0.92 to 1.05)	1.04 (0.98 to 1.09)
Simeprevir 150 mg once daily	25 mg once daily	23	1.04 (0.95 to 1.13)	1.12 (1.05 to 1.19)	1.25 (1.16 to 1.35)

n = Maximum number of subjects with data; NA = 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 coadministered drug.

[b] Comparison based on historic controls.

12.4 Microbiology

Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral 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.

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

Antiviral Activity in Cell Culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM to 2.1 nM (0.21 to 0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M [clades A, B, C, D, E, F, and G] and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM.

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). Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M (clades A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 nM to 1.01 nM (0.03 to 0.37 ng/mL) and was less active against group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

Antiviral Activity in Combination with Other Antiviral Agents

Neither dolutegravir nor rilpivirine were antagonistic to all tested anti-HIV agents or with each other when tested in combination.

Resistance

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E, or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

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 frequently observed amino acid substitutions that emerged and conferred decreased phenotypic susceptibility to rilpivirine included: L100I; K101E; V106I and A; V108I; E138K and G, Q, R; V179F and I; Y181C and I; V189I; G190E; H221Y; F227C; and M230I and L.

Virologically Suppressed Subjects: In the pooled SWORD-1 and SWORD-2 trials, 12 subjects (7 in SWORD-1 and 5 in SWORD-2) had confirmed virologic failure (HIV-1 RNA greater than 200 copies/mL) while receiving dolutegravir plus rilpivirine at any time through Week 148. Ten of the confirmed virologic failures had post-baseline resistance data, with 6 isolates showing evidence of rilpivirine resistance, and 2 with evidence of dolutegravir resistance substitutions. Six isolates showed genotypic and/or phenotypic resistance to rilpivirine with emergent NNRTI-resistance substitutions E138E/A (rilpivirine 1.6-fold change), M230M/L (rilpivirine 2-fold change), L100L/I, K101Q and E138A (rilpivirine 4.1-fold change), K101K/E (rilpivirine 1.2-fold change), K101K/E, M230M/L (rilpivirine 2-fold change), and L100L/V/M, M230M/L (rilpivirine 31-fold change). In addition, 1 virologic failure subject had NNRTI-resistance

substitutions K103N and V179I at Week 88 with rilpivirine phenotypic fold change of 5.2 but had no baseline sample.

One virologic failure isolate had emergent INSTI-resistance substitution V151V/I present post-baseline with baseline INSTI-resistance substitutions N155N/H and G163G/R (by exploratory HIV proviral DNA archive sequencing); no integrase phenotypic data were available for this isolate at virologic failure. One other subject had the dolutegravir-resistance substitution G193E at baseline and virologic failure, but no detectable phenotypic resistance (fold change = 1.02) at Week 24.

No resistance-associated substitutions were observed for the 2 subjects meeting confirmed virologic failure in the comparative current antiretroviral regimen arms at Week 48.

Cross-Resistance

Dolutegravir: The susceptibility of dolutegravir was tested against 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).

Rilpivirine: Considering all of the available cell culture and clinical data, any of the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of rilpivirine: K101E or P; E138A, G, K, R, or Q; V179L; Y181C, I, or V; Y188L; H221Y; F227C; M230I or L.

Cross-resistance in site-directed mutant virus has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I, and Y181V conferred 52 times, 15 times, and 12 times decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7 times reduced susceptibility to rilpivirine compared with 2.8 times for E138K alone. The K103N substitution did not show reduced susceptibility to rilpivirine by itself. However, the combination of K103N and L100I resulted in a 7 times reduced susceptibility to rilpivirine. In another study, the Y188L substitution resulted in a reduced susceptibility to rilpivirine of 9 times for clinical isolates and 6 times for site-directed mutants. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to rilpivirine (fold-change range: 3.7 to 554) in 38% and 66% of mutants, respectively.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 20 times higher than those in humans at the recommended dose of 50 mg once daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures approximately 17 times higher than those in humans at the recommended dose of 50 mg once daily.

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 per kg per day were administered to mice and doses of 40, 200, 500, and 1,500 mg per kg per day were administered to rats. In rats, there were no drug-related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21 (mice) and 3 (rats) times higher than those observed in humans at the recommended dose (25 mg once daily).

Mutagenesis

Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

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

Impairment of Fertility

Dolutegravir did not affect male or female fertility in rats at doses associated with exposures approximately 33 times higher than the exposures in humans at the doses of 50 mg once daily.

No human data on the effect of rilpivirine on fertility are available. In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg per kg per day, a dose of rilpivirine 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.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adult Subjects Switching to JULUCA

The efficacy of JULUCA is supported by data from 2 open-label, controlled trials (SWORD-1 [NCT02429791] and SWORD-2 [NCT02422797]) in virologically suppressed patients switching from their current antiretroviral regimen to dolutegravir plus rilpivirine.

SWORD-1 and SWORD-2 are identical 148-week, Phase 3, randomized, multicenter, parallel-group, non-inferiority trials. 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) for at least 6 months (HIV-1 RNA less than 50 copies per mL), with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine received treatment in the trials. Subjects were randomized 1:1 to continue their current antiretroviral regimen (n°=°511) or be switched to dolutegravir plus rilpivirine administered once daily (n°=°513). Subjects originally assigned to continue their current antiretroviral regimen and who remained virologically suppressed at Week 48 switched to dolutegravir plus rilpivirine at Week°52 (n°=°477).

The primary efficacy endpoint for the SWORD trials was the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL at Week 48.

At baseline, in the pooled analysis, the median age of subjects was 43 years (range: 21 to 79), 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 INSTI, respectively, as their baseline third-treatment-agent class prior to randomization. This distribution was similar between treatment arms.

The primary endpoint and other outcomes (including outcomes by key baseline covariates) for the pooled SWORD-1 and SWORD-2 trials are shown in Table 12. The virologic outcome results for SWORD-1 and SWORD-2 were similar to the pooled SWORD-1 and SWORD-2 virologic outcome results.

Table 12. Pooled Virologic Outcomes of Randomized Treatment in SWORD-1 and SWORD-2 Trials at Week 48 in Virologically Suppressed Subjects Who Switched to JULUCA (Snapshot Algorithm)

	Pooled Data	
	Dolutegravir plus Rilpivirine (n = 513)	**Current Antiretroviral Regimen (n = 511)**
HIV-1 RNA <50 copies/mL	95%	95%
Treatment Difference	-0.2% (95% CI: -3.0%, 2.5%)	

HIV-1 RNA ≥50 copies/mL	<1%	1%
Treatment Difference	-0.6 % (95% CI:-1.7%, 0.6%)	
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%
Discontinued due to adverse event or death	3%	<1%
Discontinued for other reasons[a]	1%	3%
Missing data during window but on study	0	<1%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Baseline CD4+ (cells/mm^3)		
<350	88% (n = 58)	88% (n = 52)
≥350	96% (n = 455)	96% (n = 459)
Baseline Third-Treatment-Agent Class		
INSTI	94% (n = 105)	95% (n = 97)
NNRTI	96% (n = 275)	95% (n = 278)
PI	93% (n = 133)	94% (n = 136)
Gender		
Male	95% (n = 393)	96% (n = 403)
Female	93% (n = 120)	91% (n = 108)
Race		
White	94% (n = 421)	95% (n = 400)
African-America/African Heritage/Other	99% (n = 92)	95% (n = 111)
Age (years)		
<50	96% (n = 366)	94% (n = 369)
≥50	93% (n = 147)	96% (n = 142)

INSTI = Integrase strand transfer inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease inhibitor.

[a] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Treatment differences were maintained across baseline characteristics including, CD4+ cell count, age, gender, race, and baseline third-treatment-agent class.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Each JULUCA tablet contains 50 mg of dolutegravir and 25 mg of rilpivirine, and is a pink, oval, film-coated, biconvex tablet debossed with “SV J3T” on one side.

Bottle of 30 tablets with child-resistant closure (contains a desiccant) NDC 42067-150-01

Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

This drug was imported from Canada without the authorization of ViiV Healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Severe Skin and Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop a rash. Instruct patients to immediately stop taking JULUCA and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as DRESS severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; breathing difficulty; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes; dark or tea-colored urine; pale-colored stools or bowel movements; nausea; vomiting; loss of appetite; or pain, aching, or sensitivity on the right side below the ribs). Advise patients that if hypersensitivity occurs, they will be closely monitored, laboratory tests will be ordered, and appropriate therapy will be initiated *[see Warnings and Precautions (5.1)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with rilpivirine and dolutegravir, components of JULUCA *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatotoxicity is recommended.

Embryo-Fetal Toxicity

Advise individuals of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of JULUCA with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precaution (5.3), Use in Specific Populations (8.1, 8.3)]*.

Individuals of childbearing potential taking JULUCA should be counseled on the consistent use of effective contraception *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

Depressive Disorders

Inform patients that depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with the components of JULUCA. Advise patients to seek immediate medical evaluation if they experience depressive symptoms *[see Warnings and Precautions (5.4), Adverse Reactions (6.1)]*.

Drug Interactions

JULUCA may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.5), Drug Interactions (7)]*.

Administration Instruction

Inform patients that it is important to take JULUCA once daily on a regular dosing schedule with a meal and to avoid missing doses as it can result in development of resistance. Instruct patients that if they miss a dose of JULUCA, to take it as soon as they remember with a meal. Advise patients not to double their next dose. Advise the patient a protein drink alone does not replace a meal *[see Clinical Pharmacology (12.3)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to JULUCA during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Storage

Instruct patients to store JULUCA in the original bottle to protect from moisture and keep the bottle tightly closed. Do not remove desiccant *[see How Supplied/Storage and Handling (16)]*.

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by:
GlaxoSmithKline
Durham, NC 27701

JLC:xPI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

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PATIENT INFORMATION

JULUCA (Jah-LOO-kah)

(dolutegravir and rilpivirine tablets)

What is JULUCA?

JULUCA is a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) infection in adults to replace their current anti-HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

It is not known if JULUCA is safe and effective in children.

Do not take JULUCA if you:

- have ever had an allergic reaction to a medicine that contains dolutegravir or rilpivirine.
- are taking any of the following medicines:
  - dofetilide
  - carbamazepine
  - oxcarbazepine
  - phenobarbital
  - phenytoin
  - rifampin
  - rifapentine
  - proton pump inhibitors, including:
    - esomeprazole
    - lansoprazole
    - omeprazole
    - pantoprazole sodium
    - rabeprazole
  - St. John's wort (*Hypericum perforatum*)
  - more than 1 dose of the steroid medicine dexamethasone or dexamethasone sodium phosphate

Before you take JULUCA, tell your healthcare provider about all of your medical conditions, including if you:

- have ever had a severe skin rash or an allergic reaction to medicines that contain dolutegravir or rilpivirine.
- have or have had liver problems, including hepatitis B or C infection.
- have ever had a mental health problem.
- are pregnant or plan to become pregnant. One of the medicines in JULUCA called dolutegravir may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than JULUCA if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy.
  - If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with JULUCA.
  - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with JULUCA.

- Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with JULUCA.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including JULUCA, during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take JULUCA.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - One of the medicines in JULUCA (dolutegravir) passes to your baby in your breast milk.

  Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with JULUCA. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with JULUCA.
- Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take JULUCA with other medicines.

How should I take JULUCA?

- **Take JULUCA 1 time a day exactly as your healthcare provider tells you.**
- **Always take JULUCA with a meal.** A protein drink alone does not replace a meal.
- Do not change your dose or stop taking JULUCA without talking with your healthcare provider.
- If you take an H_2-receptor antagonist (famotidine, cimetidine, nizatidine, or ranitidine), JULUCA should be taken at least 4 hours before or 12 hours after you take these medicines.
- If you take antacids, laxatives, or other products that contain aluminum, calcium carbonate, magnesium, or buffered medicines, JULUCA should be taken at least 4 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with JULUCA:
  - You may take these supplements at the same time that you take JULUCA with food.
  - If you do not take these supplements with JULUCA and food, take JULUCA at least 4 hours before or 6 hours after you take these supplements.
- Do not miss a dose of JULUCA.
- If you miss a dose of JULUCA, take it as soon as you remember with a meal. Do not take 2 doses at the same time.
- Stay under the care of a healthcare provider during treatment with JULUCA.
- Do not run out of JULUCA. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much JULUCA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of JULUCA?

JULUCA can cause serious side effects, including:

Severe skin rash and allergic reactions. Call your healthcare provider right away if you develop a rash with JULUCA**. Stop taking JULUCA and get medical help right away if you develop a rash with any of the following signs or symptoms:**

- fever
- generally ill feeling
- tiredness
- muscle or joint aches
- blisters or sores in mouth
- blisters or peeling of the skin
- redness or swelling of the eyes
- swelling of the mouth, face, lips, or tongue
- problems breathing

- **Liver problems**. People with a history of hepatitis B or C virus who have certain liver function test changes may have an increased risk of developing new or worsening changes in certain liver tests during treatment with JULUCA. Liver problems, including liver failure, have also happened in people without history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver function. **Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area
- **Depression or mood changes. Tell your healthcare provider right away or get medical help if you have any of the following symptoms:**
  - feeling sad or hopeless
  - feeling anxious or restless
  - have thoughts of hurting yourself (suicide) or have tried to hurt yourself
- **The most common side effects of JULUCA include:**
  - diarrhea
  - nausea
  - headache

These are not all the possible side effects of JULUCA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JULUCA?

- Store JULUCA at room temperature between 68°F to 77°F (20°C to 25°C).
- Store JULUCA tablets in the original bottle. Keep the bottle tightly closed and protected from moisture.
- The bottle of JULUCA contains a desiccant to help keep your medicine dry (protect it from moisture). Keep the desiccant in the bottle. Do not remove the desiccant.

Keep JULUCA and all medicines out of the reach of children.

General information about the safe and effective use of JULUCA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use JULUCA for a condition for which it was not prescribed. Do not give JULUCA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about JULUCA that is written for health professionals.

What are the ingredients in JULUCA?

Active ingredients: dolutegravir and rilpivirine.

Inactive ingredients: croscarmellose sodium, D-mannitol, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, povidone K29/32 and K30, silicified microcrystalline cellulose, sodium starch glycolate, and sodium stearyl fumarate.

The tablet film-coating contains: iron oxide red, iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

Manufactured for:

ViiV Healthcare

Durham, NC 27701

by:

GlaxoSmithKline

Durham, NC 27701

JLC:xPIL

For more information go to www.JULUCA.com or call 1-877-844-8872.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised:10/2022

This drug was imported from Canada without the authorization of ViiV Healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

---------- **ADVERSE REACTIONS** ----------

The most common adverse reactions (all grades) observed in at least 2% of subjects were diarrhea, headache, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each JULUCA tablet contains 50 mg of dolutegravir and 25 mg of rilpivirine, and is a pink, oval, film-coated, biconvex tablet debossed with "SV J3T" on one side.

Bottle of 30 tablets with child-resistant closure (contains a desiccant) NDC 49702-242-13.

Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

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FLSIP

---------- **ADVERSE REACTIONS** ----------

The most common adverse reactions (all grades) observed in at least 2% of subjects were diarrhea, headache, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each JULUCA tablet contains 50 mg of dolutegravir and 25 mg of rilpivirine, and is a pink, oval, film-coated, biconvex tablet debossed with "SV J3T" on one side.

Bottle of 30 tablets with child-resistant closure (contains a desiccant) NDC 42067-150-01

Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

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Proposed Package Label

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients	FDA Comments
10/27/2022	Juluca	Dolutegravir-rilpivirine	50-25 mg	49702-242-13	210192	ViiV Healthcare	Durham, NC 27701	Dolutegravir-rilpivirine	Aug-23	Julcua	Dolutegravir-rilpivirine	50-25 mg	42067-125-01	LifeScience Logistics, LLC	ViiV Healthcare	Durham, NC 27701	Dolutegravir-rilpivirine	n/a

Canadian to FDA Drug Comparison

Comparisons
Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Active Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Active Ingredients	Comments for FDA
dolutegravir and rilpivirine.	263286	Julcua	Dolutegravir-rilpivirine	263286	Revision: August 29, 2022	ViiV Healthcare ULC	75 Rue Queen, Suite 1400 Montreal, Quebec Canada H3C 2N6	50-25 mg	Oral Tablet, Once daily	2	dolutegravir and rilpivirine.	Juluca	Dolutegravir-rilpivirine	50-25 mg	49702-242-13	NDA210192	ViiV Healthcare Durham, NC 27701	Dolutegravir-rilpivirine	n/a

Canadian Monograph

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

ViiV Healthcare ULC
75 Rue Queen, Suite 1400
Montreal, Quebec
Canada
H3C 2N6

Date of Initial Approval:
May 17, 2018

Date of Revision:
August 29, 2022

Submission Control No: 263286

RECENT MAJOR LABEL CHANGES

Section	Date
7 Warnings and Precautions, 7.1.1 Pregnant Women	08/2022
7 Warnings and Precautions, 7.1.2 Breast-feeding	08/2022

TABLE OF CONTENTS

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):

- Drugs with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to dofetilide, an antiarrhythmic agent, or the potassium channel blocker fampridine (also known as dalfampridine)
- 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)

4 DOSAGE AND ADMINISTRATION

4.1 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.
- Perform pregnancy testing before initiation of JULUCA in individuals of childbearing potential.

4.2 Recommended Dose and Dosage Adjustment

Adults
The recommended dose of JULUCA in adults is one tablet once daily taken orally with a meal (see 10.3 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 10.3 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 10.3 Pharmacokinetics, Special Populations and Conditions, *Hepatic Insufficiency*).

4.5 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.

5 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. 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.

6 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.

7 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.

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.

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 8 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 2 CONTRAINDICATIONS, 9 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 2 CONTRAINDICATIONS, 9 DRUG INTERACTIONS, 10 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 8 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 2 CONTRAINDICATIONS).

Reproductive Health: Female and Male Potential

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 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 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 16 NON-CLINICAL TOXICOLOGY). Women of childbearing potential (WOCBP) should be informed about the potential risk of neural tube defects with dolutegravir and counselled about the use of effective contraception. It is recommended that pregnancy testing is conducted prior to initiation of JULUCA If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on JULUCA, the risks and benefits of continuing JULUCA versus switching to another antiretroviral regimen should be discussed with the patient. Factors to consider should include feasibility of switching tolerability, ability to maintain viral suppression, actual gestational age, risk of transmission to the infant and the available data around the potential risk of neural tube defects and other pregnancy outcomes for dolutegravir and alternative antiretroviral drugs.

In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was identified with exposure to dolutegravir compared to non-dolutegravir-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.03,-0.30). In the same study, an increased risk of neural tube defects was not identified in women who started dolutegravir during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-dolutegravir-containing regimens during pregnancy. A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As most neural tube defects occur within the first 4 weeks of fetal development (approximately 6 weeks after the last menstrual period) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Data analyzed to date from other sources including the Antiretroviral Pregnancy Registry (APR), clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with dolutegravir. From the APR, one neural tube defect has been identified in 312 (0.32%) live births with periconceptual exposures to dolutegravir.

More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes and the APR continues to monitor for DTG safety in pregnancy.

Dolutegravir and rilpivirine use during pregnancy have been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 700 and 675 women, respectively. Available human data from the APR do not show an increased risk of major birth defects for dolutegravir or rilpivirine compared to the background rate.

Dolutegravir readily crosses the placenta in humans. In HIV-infected pregnant women, the median (range) fetal 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.

Based on prospective reports to the APR of over 700 exposures to dolutegravir during pregnancy resulting in live births (including over 450 exposed in the first trimester), there was no difference between the overall risk of birth defects for dolutegravir when compared to the background birth defect rate of 2.7% and 4.17% from two population based surveillance systems (Metropolitan Atlanta Congenital Defects Program (MACDP) with defects of 2.72 per 100 live births and the Texas Birth Defects Registry (TBDR) with 4.17 per 100 live births). The prevalence of defects in live births was 3.5% (95% CI: 2.0% to 5.6%) following first trimester exposure to dolutegravir-containing regimens and 4.2% (95% CI: 2.2% to 7.2%) following second/third trimester exposure to dolutegravir-containing regimens.

Based on prospective reports to the APR of over 675 exposures to rilpivirine during pregnancy resulting in live births (including 495 exposed in the first trimester), there was no difference between the overall risk of birth defects for rilpivirine compared with the background birth defect rates of 2.7% and 4.17%

from the MACPD and TBDR, respectively. The prevalence of defects in live births was 1.4% (95% CI: 0.6% to 2.9%) and 1.5% (95% CI: 0.3% to 4.5%) following first and second/third trimester exposure, respectively, to rilpivirine-containing regimens.

In reproductive toxicity studies in animals, 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 16 NON-CLINICAL TOXICOLOGY).

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 (see Pharmacokinetics, Special Populations and Conditions, Pregnancy and Postpartum).

7.1.2 Breast-feeding

HIV-1-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. 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 present in human milk. HIV-1-infected mothers should be instructed not to breast-feed if they are receiving JULUCA.

7.1.3 Pediatrics

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

7.1.4 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.

8 ADVERSE REACTIONS

8.1 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, including additional follow-up through week 148. 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 (Early Switch). Subjects initially randomized to continue their current antiretroviral regimen and who remained virologically suppressed at Week 48 switched to dolutegravir plus rilpivirine at Week 52 (Late Switch). The rates of adverse events leading to discontinuation in the pooled analysis through week 48 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 through week 48 were psychiatric disorders; 2% of patients receiving dolutegravir plus rilpivirine and less than 1% on the current antiretroviral regimen. In the pooled analyses, the rate of adverse events leading to discontinuation through Week 148 was 8%.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

In the Week 148 pooled analyses, nausea and headache (all grades) were observed in 2% of patients (n = 8 and n = 11, respectively) who received DTG plus RPV from study start.

8.3 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.

8.3.1 Clinical Trial Adverse Reactions (Pediatrics)

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

8.4 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.

For subjects in the pooled Early Switch DTG+RPV and Late Switch DTG+RPV groups through Week 148, the majority of post-Baseline emergent clinical chemistry toxicities were Grade 1 or Grade 2 in intensity and the proportions of subjects with any Grade 3 or Grade 4 clinical chemistry toxicities were 4% or less.

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

Changes in Serum Creatinine: Increases in serum creatinine occurred within the first four weeks of treatment with dolutegravir plus rilpivirine and remained stable through 148 weeks. Mean (SD) changes from baseline of 8.22 μmol/L (9.41) and 9.86 μmol/L (10.40) were observed after 48 weeks and 148

weeks of treatment, respectively. 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 10.2 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 10.3 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.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

8.5 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

9 DRUG INTERACTIONS

9.2 Drug Interactions 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.

9.3 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 (for example dofetilide, fampridine (also known as dalfampridine) [see 2 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 10.3 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 10.3 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
Antiarrhythmic: Dofetilide	Effect of dolutegravir: Dofetilide ↑	Co-administration of JULUCA with dofetilide is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentrations.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug*	Clinical comment
Potassium channel blocker: Fampridine (also known as dalfampridine	Fampridine/Dalfampridine↑	Co-administration is contraindicated with JULUCA due to potential for seizures associated with fampridine/dalfampridine.
Anticonvulsants: Carbamazepine, Oxcarbazepine, Phenytoin, Phenobarbital	Effect of carbamazepine: Dolutegravir ↓ Rilpivirine ↓	Co-administration is contraindicated.
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.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug*	Clinical comment
Calcium and Iron supplements, including multivitamins containing calcium or iron[b] (Non-antacid)	Calcium: Dolutegravir ↓ Iron: Dolutegravir ↓	When taken with food, JULUCA and calcium and/or iron supplements or multivitamins containing calcium and/or iron can be taken at the same time. Under fasting conditions, JULUCA should be taken at least 4 hours before or 6 hours after taking calcium or iron supplements (non-antacids).
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.
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)
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)

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}
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)
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}
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}
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	↔[b]	↔[b]	↔[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	↔[b]	↔[b]	↔[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)
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.

9.5 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 10 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.

9.6 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.

9.7 Drug-Laboratory Test Interactions

No Drug-Laboratory test interactions have been identified.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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.

10.3 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 14.2 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 14.2 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. Therefore, to achieve optimal exposure, EDURANT should be taken with a meal (see 4 DOSAGE AND ADMINISTRATION)

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.

Pregnancy and Breast-feeding:

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 with 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 21%, 29% and 35%, respectively, lower as compared with postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h} and C_{min} values were 20%, 31% and 42%, respectively, lower as compared with postpartum. There are no pharmacokinetic data on the use of dolutegravir in pregnancy.

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. There is limited information on dolutegravir 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.

11 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.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Dolutegravir

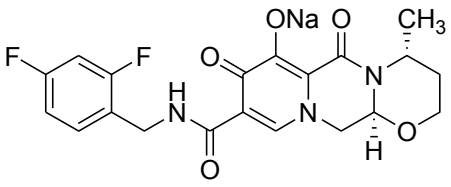
Drug Substance

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

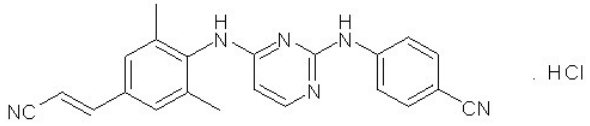
Drug Substance

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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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)

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, randomized, 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 randomized 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 initially randomized 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 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%)

~~14.2~~ 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.

At Week 148 in the pooled SWORD-1 and SWORD-2 trials, 84% of subjects who received dolutegravir plus rilpivirine from 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 from study start.

14.2 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

15 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
Overall, 11 subjects receiving dolutegravir plus rilpivirine in the pooled SWORD-1 and SWORD-2 trials had confirmed virologic failure through Week 148.

Through Week 48 with comparative data, two subjects receiving dolutegravir plus rilpivirine and two subjects continuing their current antiretroviral regimen had confirmed virologic failure. 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 (FC = 0.75) at Week 36, had no INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir (FC 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 (FC= 1.02) at Week 24. No resistance-associated substitutions were observed for the other 2 subjects in the comparative current antiretroviral regimen arms.

From Week 48 through Week 148, in the pooled analyses, 9 additional subjects receiving dolutegravir plus rilpivirine had confirmed virologic failure at any time. Eight of the 9 subjects had resistance testing results available; 6 of the 8 subjects had postbaseline results and NNRTI resistance-associated substitutions at virologic failure. These 6 subjects are further described below.

Four Subjects Receiving Dolutegravir plus Rilpivirine from Study Start: At Week 88, one subject had the NNRTI resistance-associated substitution mixture E138E/A with no decreased susceptibility to rilpivirine (FC= 1.6), and a second subject had K103N with rilpivirine FC= 5.2. Neither subject had INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir. At Week 100, a third subject with baseline NNRTI resistance-associated substitutions K101E and E138A had M230M/L in addition to K101E and E138A with rilpivirine FC = 31. Integrase resistance testing failed at virologic failure. At Week 112, a fourth subject had M230M/L mixture with rilpivirine FC= 2 and had INSTI polymorphic substitutions E157Q, G193E, and T97T/A at baseline; at virologic failure E157Q and G193E were still present, while T97T/A was no longer observed and there was no decreased susceptibility to dolutegravir (FC= 1.5).

Two Subjects Receiving Dolutegravir plus Rilpivirine from Week 52: At Week 64, one subject had integrase substitutions N155H and G163G/R at baseline and only polymorphic integrase V151I/V mixture at virologic failure, and no NNRTI resistance. Integrase phenotype assay failed for this subject, and HIV-1 RNA was less than 50 copies per mL at the withdrawal visit. At Week 136, a second 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 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.

16 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.

17 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).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]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).
  - fampridine (also known as dalfampridine) to treat multiple sclerosis.
  - 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.
- Taking JULUCA at the time of becoming pregnant, or during the first 12 weeks of pregnancy, may increase the risk of a type of birth defect, called neural tube defect, such as spina bifida (malformed spinal cord).
- 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. A small amount of the ingredients in JULUCA can also pass into your breast milk. If you are taking JULUCA, do not breastfeed.

Other warnings you should know about:

JULUCA will not stop you from passing HIV to others, although the risk is lower if you take your HIV medicine as instructed by your healthcare professional. 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional recommends. Don’t stop unless your healthcare professional advises you to.

Overdose:

If you think you, or a person you are caring for, have taken too much JULUCA, contact a 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 healthcare professional 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.		✓ ✓ ✓ ✓ ✓	

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	
Liver problems and blood test results: • Inflammation (Hepatitis) • Bilirubin increase (substance produced by liver) • Increase of muscle enzymes (CPK) • an increase in a kidney function test result (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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) 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(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.viivhealthcare.ca, or by calling 1-877-393-8448.

This leaflet was prepared by ViiV Healthcare ULC.

Last Revised August 29, 2022

Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Product Details for NDA 210192

JULUCA (DOLUTEGRAVIR SODIUM; RILPIVIRINE HYDROCHLORIDE)
EQ 50MG BASE;EQ 25MG BASE
Marketing Status: Prescription

Active Ingredient: DOLUTEGRAVIR SODIUM; RILPIVIRINE HYDROCHLORIDE
Proprietary Name: JULUCA
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 50MG BASE;EQ 25MG BASE
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N210192
Product Number: 001
Approval Date: Nov 21, 2017
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=210192&Appl_type=N)