▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Juluca 50 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir and rilpivirine hydrochloride equivalent to 25 mg rilpivirine.

Excipient with known effect
Each film-coated tablet contains 52 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pink, oval, biconvex tablets, approximately 14 x 7 mm, debossed with 'SV J3T' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Juluca is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor (see section 5.1).

4.2 Posology and method of administration

Juluca should be prescribed by physicians experienced in the management of HIV infection.

Posology

The recommended dose of Juluca is one tablet once daily. Juluca must be taken with a meal (see section 5.2).

Separate preparations of dolutegravir or rilpivirine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated (see section 4.5). In these cases the physician should refer to the Summary of Product Characteristics for these medicinal products.

Missed doses
If the patient misses a dose of Juluca, the patient should take Juluca with a meal as soon as possible, providing the next dose is not due within 12 hours. If the next dose is due within 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If a patient vomits within 4 hours of taking Juluca, another Juluca tablet should be taken with a meal. If a patient vomits more than 4 hours after taking Juluca, the patient does not need to take another dose of Juluca until the next regularly scheduled dose.

Elderly
There are limited data available on the use of Juluca in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2).

Renal impairment
No dosage adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease, the combination of Juluca with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population (see section 5.2).

Hepatic impairment
No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). Juluca should be used with caution in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh score C); therefore Juluca is not recommended in these patients (see section 5.2).

Paediatric population
The safety and efficacy of Juluca in children and adolescents aged less than 18 years have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

Pregnancy
The safety and efficacy of Juluca in pregnancy have not yet been established. Limited data are available regarding the use of dolutegravir during pregnancy. Lower exposures of dolutegravir and rilpivirine were observed during pregnancy. No recommendations for dose adjustments can be made for Juluca. Therefore, use of Juluca during pregnancy is not recommended (see sections 4.4, 4.6, 5.1 and 5.2).

Method of administration

Oral use
Juluca must be taken orally, once daily **with a meal** (see section 5.2). It is recommended that the film-coated tablet be swallowed whole with water and not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Co-administration with the following medicinal products:
- dofetilide;
- carbamazepine, oxcarbazepine, phenobarbital, phenytoin;
- rifampicin, rifapentine;
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole;
- systemic dexamethasone, except as a single dose treatment;
- St John's wort (*Hypericum perforatum*).

4.4 Special warnings and precautions for use

Transmission of HIV

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.

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Juluca should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with Juluca after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Cardiovascular

At supra-therapeutic doses (75 and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG) (see sections 4.5 and 5.1). Rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Juluca should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes.

Opportunistic infections

Patients should be advised that Juluca does not cure HIV infection and that they 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.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, biphosphonates, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Patients with hepatitis B or C

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

Interactions with other medicinal products

Juluca should not be administered with other antiretroviral medicinal products for the treatment of HIV (see section 4.5).

Juluca should not be co-administered at the same time as H_2-receptor antagonists. These medicinal products are recommended to be administered 12 hours before or 4 hours after Juluca (see section 4.5).

Juluca should not be co-administered at the same time as antacids. These medicinal products are recommended to be administered 6 hours before or 4 hours after Juluca (see section 4.5).

Calcium or iron supplements, or multivitamins should be co-administered at the same time as Juluca, with a meal. If calcium or iron supplements, or multivitamins cannot be taken at the same time as Juluca, these supplements are recommended to be administered 6 hours before or 4 hours after taking Juluca (see section 4.5).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of Juluca with metformin, to maintain glycaemic control (see section 4.5). Metformin is eliminated renally and therefore it is of importance to monitor renal function when co-treated with Juluca. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

Juluca should not be taken with any other medicinal product containing dolutegravir or rilpivirine, except in case of co-administration with rifabutin (see section 4.5).

Pregnancy

The safety and efficacy of Juluca in pregnancy have not yet been established. Limited data are available regarding the use of dolutegravir during pregnancy. Lower exposures of dolutegravir or rilpivirine were observed when taken once daily, in combination with a background regimen, during pregnancy. In phase 3 studies, lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure. No recommendations for dose adjustments can be made for Juluca. Therefore, use of Juluca during pregnancy is not recommended (see sections 4.6, 5.1 and 5.2).

Immune Reactivation Syndrome

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

Excipients

Juluca contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Juluca is intended for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral medicinal products for the treatment of HIV. Therefore, information regarding drug-drug interactions with other antiretroviral medicinal products is not provided. Juluca contains dolutegravir and rilpivirine, therefore any interactions identified with these active substances are relevant to Juluca. Interaction studies have only been performed in adults.

Effect of other medicinal products on the pharmacokinetics of dolutegravir and rilpivirine

Dolutegravir is eliminated mainly through metabolism by uridine diphosphate glucuronosyl transferase (UGT)1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, cytochrome P450 (CYP)3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP); therefore medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of

dolutegravir (see Table 1). Co-administration of Juluca and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 1).

The absorption of dolutegravir is reduced by certain anti-acid medicinal products (see Table 1).

Rilpivirine is primarily metabolised by CYP3A. Medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see section 5.2). Co-administration of Juluca with medicinal products that induce CYP3A may result in decreased plasma concentrations of rilpivirine, which could reduce the therapeutic effect of Juluca (see Table 1). Co-administration of Juluca with medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine (see Table 1).

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

Effect of dolutegravir and rilpivirine on the pharmacokinetics of other medicinal products

Based on *in vivo* and/or *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (for more information see section 5.2).

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1). *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 or MATE-1 (e.g. dofetilide, metformin) (see Table 1 and sections 4.3 and 4.4).

In vitro, dolutegravir inhibited the renal uptake transporters, organic anion transporters (OAT)1 and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied *in vivo*. Dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OAT3.

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

Rilpivirine inhibits P-gp *in vitro* (IC_{50} is 9.2 μM). In a clinical study, rilpivirine did not significantly affect the pharmacokinetics of digoxin. However, it may not be completely excluded that rilpivirine can increase the exposure to other medicinal products transported by P-gp that are more sensitive to intestinal P-gp inhibition, e.g. dabigatran etexilate.

Rilpivirine is an *in vitro* inhibitor of the transporter MATE-2K with an IC_{50} of < 2.7 nM. The clinical implications of this finding are currently unknown.

Interaction table

Selected established and theoretical interactions between dolutegravir, rilpivirine and co-administered medicinal products are listed in Table 1.
(increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "Cτ").

Table 1: Drug Interactions

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**

Antiviral active substances		
Tenofovir disoproxil / Dolutegravir[1]	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% Cτ ↓ 8% Tenofovir ↔	No dose adjustment is required.
Tenofovir disoproxil / Rilpivirine[1,2]	Rilpivirine AUC ↔ C_{min} ↔ C_{max} ↔ Tenofovir AUC ↑ 23% C_{min} ↑ 24% C_{max} ↑ 19%	
Tenofovir alafenamide / Dolutegravir	Dolutegravir ↔ (Not studied)	No dose adjustment is required.
Tenofovir alafenamide / Rilpivirine[1]	Rilpivirine ↔	
Lamivudine/ Dolutegravir	Dolutegravir ↔	No dose adjustment is required.
Lamivudine/ Rilpivirine	Rilpivirine ↔ (Not studied)	
Entecavir/ Dolutegravir	Dolutegravir ↔ (Not studied)	No dose adjustment is required.
Entecavir/ Rilpivirine	Rilpivirine ↔ (Not studied)	
Boceprevir/ Dolutegravir[1]	Dolutegravir ↔ AUC ↑ 7% C_{max} ↑ 5% Cτ ↑ 8% Boceprevir ↔ (historical controls).	No dose adjustment is required.
Boceprevir/ Rilpivirine	Rilpivirine ↑ (Not studied, inhibition of CYP3A enzymes).	
Daclatasvir/ Dolutegravir[1]	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	No dose adjustment is required.
Daclatasvir/ Rilpivirine	Rilpivirine ↔	

Simeprevir/ Dolutegravir Simeprevir/ Rilpivirine	Dolutegravir ↔ Rilpivirine ↔ AUC ↔ C_{min} ↑ 25% C_{max} ↔ Simeprevir ↔ AUC ↔ C_{min} ↔ C_{max} ↑ 10%	No dose adjustment is required.
Sofosbuvir / Dolutegravir[1] Sofosbuvir / Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ AUC ↔ C_{min} ↔ C_{max} ↔ Sofosbuvir ↔ AUC ↔ C_{max} ↑ 21% Sofosbuvir metabolite GS-331007 ↔ AUC ↔ C_{max} ↔	No dose adjustment is required.
Ledipasvir/Sofosbuvir / Dolutegravir[1] Ledipasvir/Sofosbuvir / Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ AUC ↓ 5% C_{min} ↓ 7% C_{max} ↓ 3% Ledipasvir ↔ AUC ↑ 2% C_{min} ↑ 2% C_{max} ↑ 1% Sofosbuvir ↔ AUC ↑ 5% C_{max} ↓ 4% Sofosbuvir metabolite GS-331007 ↔ AUC ↑ 8% C_{min} ↑ 10% C_{max} ↑ 8%	No dose adjustment is required.
Sofosbuvir/ Velpatasvir/ Dolutegravir[1] Sofosbuvir/ Velpatasvir/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ AUC ↔ C_{min} ↔ C_{max} ↔ Sofosbuvir ↔ AUC ↔ C_{max} ↔	No dose adjustment is required.

	Sofosbuvir metabolite GS-331007 ↔ AUC ↔ C_{min} ↔ C_{max} ↔ Velpatasvir ↔ AUC ↔ C_{min} ↔ C_{max} ↔	
Ribavirin/ Dolutegravir Ribavirin/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ (Not studied)	No dose adjustment is required.
Other active substances		
Antiarrhythmics		
Dofetilide/ Dolutegravir	Dofetilide ↑ Not studied. Potential increase via inhibition of OCT2 transporter.	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration (see section 4.3).
Digoxin/ Dolutegravir Digoxin/ Rilpivirine[1]	Dolutegravir ↔ (Not studied) Rilpivirine ↔ Digoxin AUC ↔ C_{min} NA C_{max} ↔	No dose adjustment is required.
Anticonvulsants		
Carbamazepine/ Dolutegravir[1] Carbamazepine/ Rilpivirine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% Cτ ↓ 73% Rilpivirine↓ Not studied. Significant decreases in rilpivirine plasma concentrations are expected (induction of CYP3A enzymes).	Metabolic inducers may significantly decrease dolutegravir/rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of Juluca with these metabolic inducers is contraindicated (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbital/ Dolutegravir Oxcarbazepine Phenytoin Phenobarbital/ Rilpivirine	Dolutegravir ↓ Not studied. Decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected. Rilpivirine ↓ Not studied. Significant decreases in rilpivirine plasma concentrations are expected	Metabolic inducers may significantly decrease dolutegravir/rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of Juluca with these metabolic inducers is contraindicated (see section 4.3).

	(induction of CYP3A enzymes).	
Azole anti-fungals		
Ketoconazole/ Dolutegravir Ketoconazole/ Rilpivirine[1,2]	Dolutegravir ↔ (Not studied) Rilpivirine AUC ↑ 49% C_{min} ↑ 76% C_{max} ↑ 30% (inhibition of CYP3A enzymes). Ketoconazole AUC ↓ 24% C_{min} ↓ 66% C_{max} ↔ (induction of CYP3A due to high rilpivirine dose in the study).	No dose adjustment is required.
Fluconazole Itraconazole Isavuconazole Posaconazole Voriconazole/ Dolutegravir Fluconazole Itraconazole Isavuconazole Posaconazole Voriconazole/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↑ Not studied. May cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes).	No dose adjustment is required.
Herbal products		
St. John's wort/ Dolutegravir St. John's wort/ Rilpivirine	Dolutegravir ↓ Not studied. Decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected. Rilpivirine ↓ Not studied. Significant decreases in rilpivirine plasma concentrations are expected (induction of CYP3A enzymes).	Co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of Juluca. Co-administration of Juluca with St. John's wort is contraindicated (see section 4.3).
Proton pump inhibitors		
Omeprazole Lansoprazole	Dolutegravir ↔ (Not studied)	Co-administration may significantly decrease rilpivirine plasma concentration. This may result in

Rabeprazole Pantoprazole Esomeprazole/ Dolutegravir		loss of therapeutic effect of Juluca. Co-administration of Juluca with proton pump inhibitors is contraindicated (see section 4.3).
Omeprazole/ Rilpivirine[1,2]	Rilpivirine AUC ↓ 40% C_{min} ↓ 33% C_{max} ↓ 40% (reduced absorption due to gastric pH increase). Omeprazole AUC ↓ 14% C_{min} NA C_{max} ↓ 14%	
Lansoprazole Rabeprazole Pantoprazole Esomeprazole/ Rilpivirine	Rilpivirine ↓ Not studied. Significant decreases in rilpivirine plasma concentrations are expected (reduced absorption due to gastric pH increase).	
H_2-recepter antagonists		
Famotidine Cimetidine Nizatidine Ranitidine/ Dolutegravir	Dolutegravir ↔ (Not studied)	The combination of Juluca and H_2-receptor antagonists should be used with particular caution. Only H_2-receptor antagonists that can be dosed once daily should be used. H_2-receptor antagonists should be taken well separated in time from the administration of Juluca (minimum 4 hours after or 12 hours before)
Famotidine/ Rilpivirine[1,2] 40 mg single dose taken 12 hours before rilpivirine	Rilpivirine AUC ↓ 9% C_{min} NA C_{max} ↔	
Famotidine/ Rilpivirine[1,2] 40 mg single dose taken 2 hours before rilpivirine	Rilpivirine AUC ↓ 76% C_{min} NA C_{max} ↓ 85% (reduced absorption due to gastric pH increase).	
Famotidine/ Rilpivirine[1,2] 40 mg single dose taken 4 hours after rilpivirine	Rilpivirine AUC ↑ 13% C_{min} NA C_{max} ↑ 21%	
Cimetidine Nizatidine Ranitidine/ Rilpivirine	Rilpivirine ↓ Not studied. Significant decreases in rilpivirine plasma concentrations are	

	expected (reduced absorption due to gastric pH increase).	
Antacids and supplements		
Antacids (e.g., aluminium magnesium hydroxide, and/or calcium carbonate)/ Dolutegravir[1] Antacids (e.g., aluminium magnesium hydroxide, and/or calcium carbonate)/ Rilpivirine	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% C_{24} ↓ 74% (Complex binding to polyvalent ions). Rilpivirine ↓ Not studied. Significant decreases in rilpivirine plasma concentrations are expected (reduced absorption due to gastric pH increase).	The combination of Juluca and antacids should be used with particular caution. Antacids should be taken well separated in time from the administration of Juluca (minimum 6 hours before or 4 hours after).
Calcium supplements/ Dolutegravir[1]	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions).	The combination of Juluca and supplements should be used with particular caution. Calcium supplements, iron supplements or multivitamins should be co-administered at the same time as Juluca with a meal. If calcium supplements, iron supplements or multivitamins cannot be taken at the same time as Juluca, these supplements should be taken well separated in time from the administration of Juluca (minimum 6 hours before or 4 hours after).
Iron supplements/ Dolutegravir[1]	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56% (Complex binding to polyvalent ions).	
Multivitamin/ Dolutegravir[1]	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions).	
Corticosteroids		
Prednisone/ Dolutegravir[1] Prednisone/ Rilpivirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% Cτ ↑ 17% Rilpivirine ↔ (Not studied)	No dose adjustment is required.
Dexamethasone/ Dolutegravir Dexamethasone/ Rilpivirine (systemic, except for single dose use)	Dolutegravir ↔ (Not studied) Rilpivirine ↓ Not studied. Dose dependent decreases in rilpivirine plasma concentrations are expected (induction of CYP3A enzymes).	Co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of Juluca. Co-administration of Juluca with systemic dexamethasone is contraindicated (except as a single dose) see section 4.3. Alternatives should be considered, particularly for long-term use.
Antidiabetics		

Metformin/ Dolutegravir[1]	Metformin ↑ AUC ↑ 79% C_{min} NA C_{max} ↑ 66%	A dose adjustment of metformin should be considered when starting and stopping co-administration of Juluca with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when co-administered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4).
Metformin/ Rilpivirine[1]	Metformin AUC ↔ C_{min} NA C_{max} ↔	
Antimycobacterials		
Rifampicin/ Dolutegravir[1]	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓72% (induction of UGT1A1 and CYP3A enzymes).	Co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of Juluca. Co-administration of Juluca with rifampicin is contraindicated (see section 4.3).
Rifampicin/ Rilpivirine[1,2]	Rilpivirine AUC ↓ 80% C_{min} ↓ 89% C_{max} ↓ 69% (induction of CYP3A enzymes). Rifampicin AUC ↔ C_{min} NA C_{max} ↔ 25-desacetyl-rifampicin AUC ↓ 9% C_{min} NA C_{max} ↔	
Rifabutin/ Dolutegravir[1]	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes).	Co-administration is likely to cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). When Juluca is co-administered with rifabutin, an additional 25 mg tablet of rilpivirine per day should be taken at the same time with Juluca, for the duration of the rifabutin co-administration (a separate formulation of rilpivirine is available for this dose adjustment, see section 4.2).
Rifabutin/ Rilpivirine[1] 300 mg once daily[2]	Rifabutin AUC ↔ C_{min} ↔ C_{max} ↔ 25-*O*-desacetyl-rifabutin AUC ↔ C_{min} ↔ C_{max} ↔	
300 mg once daily (+ 25 mg once daily rilpivirine)	Rilpivirine AUC ↓ 42% C_{min} ↓ 48% C_{max} ↓ 31%	
300 mg once daily	Rilpivirine	

(+ 50 mg once daily rilpivirine)	AUC ↑ 16%* C_{min} ↔* C_{max} ↑ 43%* * compared to 25 mg once daily rilpivirine alone (induction of CYP3A enzymes).	
Rifapentine/ Dolutegravir Rifapentine/ Rilpivirine	Dolutegravir ↓ (Not studied) Rilpivirine ↓ Not studied. Significant decreases in rilpivirine plasma concentrations are expected.	Co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of Juluca (induction of CYP3A enzymes). Co-administration of Juluca with rifapentine is contraindicated (see section 4.3).
Antimalarials		
Artemether/ Lumefantrine/ Dolutegravir Artemether/ Lumefantrine/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↓ Not studied. Decreased exposure of rilpivirine is expected (induction of CYP3A enzymes).	The combination of Juluca and artemether/lumefantrine should be used with caution.
Atovaquone/ Proguanil/ Dolutegravir Atovaquone/ Proguanil/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ (Not studied).	No dose adjustment is required.
Macrolide antibiotics		
Clarithromycin Erythromycin /Dolutegravir Clarithromycin Erythromycin /Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↑ Not studied. Increased exposure of rilpivirine is expected (inhibition of CYP3A enzymes).	Where possible, alternatives such as azithromycin should be considered.
Oral contraceptives		
Ethinyl estradiol (EE)[1] and Norelgestromin (NGMN)[1] / Dolutegravir	Dolutegravir ↔ EE ↔ AUC ↑ 3% C_{max} ↓ 1% NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir or rilpivirine did not change ethinyl estradiol and norelgestromin (dolutegravir) or norethindrone (rilpivirine) plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is required when co-administered with Juluca.

Ethinyl estradiol (EE)[1] and Norethindrone[1]/ Rilpivirine	Rilpivirine ↔* EE ↔ AUC ↔ C_{min} ↔ C_{max} ↑ 17% Norethindrone ↔ AUC ↔ C_{min} ↔ C_{max} ↔ *based on historic controls.	
Analgesics		
Methadone/ Dolutegravir[1]	Dolutegravir ↔ Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% Cτ ↓ 1%	No dose adjustments are required when initiating co-administration of methadone with Juluca. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Methadone / Rilpivirine[1]	Rilpivirine: AUC: ↔* C_{min}: ↔* C_{max}: ↔* R(-) methadone: AUC: ↓ 16% C_{min}: ↓ 22% C_{max}: ↓ 14% *based on historic controls.	
Paracetamol/ Dolutegravir	Dolutegravir ↔ (Not studied)	No dose adjustment is required.
Paracetamol / Rilpivirine[1,2]	Rilpivirine AUC ↔ C_{min} ↑ 26% C_{max} ↔ Paracetamol AUC ↔ C_{min} NA C_{max} ↔	
Anticoagulants		
Dabigatran etexilate/ Dolutegravir	Dolutegravir ↔ (Not studied)	The combination of Juluca and dabigatran etexilate should be used with caution.
Dabigatran etexilate/ Rilpivirine	Rilpivirine ↔ Not studied. Dabigatran etexilate ↑ A risk for increases in dabigatran plasma concentrations cannot be excluded	

	(inhibition of intestinal P-gp).	
HMG CO-A reductase inhibitors		
Atorvastatin/ Dolutegravir Atorvastatin/ Rilpivirine[1,2]	Dolutegravir ↔ (Not studied) Rilpivirine AUC ↔ C_{min} ↔ C_{max} ↓ 9% Atorvastatin AUC ↔ C_{min} ↓ 15% C_{max} ↑ 35%	No dose adjustment is required.
Phosphodiesterase type 5 (PDE-5) inhibitors		
Sildenafil / Dolutegravir Sildenafil/ Rilpivirine[1,2]	Dolutegravir ↔ Rilpivirine AUC ↔ C_{min} ↔ C_{max} ↔ Sildenafil AUC ↔ C_{min} NA C_{max} ↔	No dose adjustment is required.
Vardenafil Tadalafil/ Dolutegravir Vardenafil Tadalafil/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ (Not studied)	No dose adjustment is required.

[1] The interaction between dolutegravir and/or rilpivirine and the medicinal product was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

[2] 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.

NA = Not applicable

QT prolonging medicinal products

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products that prolong the QTc interval of the ECG. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG (see section 5.1). Juluca should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of dolutegravir or rilpivirine in pregnant women. The effect of Juluca on human pregnancy is unknown.

In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. Animal studies with dolutegravir or rilpivirine do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Lower exposures of dolutegravir and rilpivirine were observed during pregnancy (see sections 4.2, 4.4, 5.1, 5.2).

The use of Juluca during pregnancy is not recommended.

Breast-feeding

It is unknown whether dolutegravir or rilpivirine are excreted in human milk. Available toxicological data in animals has shown excretion of dolutegravir and rilpivirine in milk. In lactating rats that received a single oral dose of dolutegravir 50 mg/kg at 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than blood. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

There are no data on the effects of dolutegravir or rilpivirine on human male or female fertility. Animal studies indicate no clinically relevant effects on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that fatigue, dizziness and somnolence have been reported during treatment with the components of Juluca. The clinical status of the patient and the adverse reaction profile of Juluca should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

Clinical safety data with Juluca is limited. The most frequently reported adverse reactions considered possibly or probably related to the combined administration of dolutegravir plus rilpivirine in 513 HIV-1 infected subjects in the Phase III clinical trials (see section 5.1), were diarrhoea (2%) and headache (2%).

The most severe adverse reaction, possibly related to the treatment with dolutegravir (from pooled from Phase IIb and Phase III clinical studies), seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions considered at least possibly related to treatment with the components of Juluca from clinical studies and post-marketing experience are listed in Table 2 by body system, organ class and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 2: Tabulated summary of adverse reactions to Juluca based on clinical study and post-marketing experience with Juluca and its individual components

System Organ Class (SOC)	Frequency category*	Adverse drug reactions
Blood and lymphatic systems disorders:	common	decreased white blood cell count decreased haemoglobin decreased platelet count
Immune system disorders	uncommon	hypersensitivity (see section 4.4)
	not known	immune reconstitution syndrome
Metabolism and nutrition disorders	very common	increased total cholesterol (fasted) increased LDL cholesterol (fasted)
	common	decreased appetite increased triglycerides (fasted)
Psychiatric disorders	very common	insomnia
	common	abnormal dreams depression sleep disorders depressed mood anxiety
	uncommon	suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)
Nervous system disorders	very common	headache dizziness
	common	somnolence
Gastrointestinal disorders	very common	nausea increased pancreatic amylase diarrhoea
	common	abdominal pain vomiting flatulence increased lipase abdominal discomfort upper abdominal pain dry mouth
Hepatobiliary disorders	very common	increased transaminases (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations)
	common	increased bilirubin
	uncommon	hepatitis

	rare	acute hepatic failure**
Skin and subcutaneous tissue disorders	common	rash pruritus
Musculoskeletal and connective tissue disorders	uncommon	arthralgia myalgia
General disorders and administration site conditions	common	fatigue
Investigations	common	creatine phosphokinase (CPK) elevations
* Frequencies are assigned based on the maximum frequencies observed in the pooled SWORD studies or studies with the individual components ** This adverse reaction was identified through post-marketing surveillance for dolutegravir in combination with other ARVs. The frequency category of rare was estimated based on post-marketing reports.		

Description of selected adverse reactions

Changes in laboratory biochemistries

Dolutegravir and rilpivirine have been associated with increases in serum creatinine occuring in the first week of treatment when administered with other antiretroviral medicinal products. Increases in serum creatinine occurred within the first four weeks of treatment with Juluca and remained stable through 48 weeks. A mean change from baseline of 8.22 μmol/L (range -26.5 to 51.2 μmol/L) was observed after 48 weeks treatment. These changes are related to inhibition of active transport, and are not considered to be clinically relevant as they do not reflect a change in glomerular filtration rate.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom

the Yellow Card Scheme Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland

HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

No specific symptoms or signs have been identified following acute overdose with dolutegravir or rilpivirine apart from those listed as adverse reactions.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of Juluca. If overdose occurs, the patient should be treated supportively with appropriate monitoring, including monitoring of vital signs and ECG (QT interval), as necessary. As dolutegravir and rilpivirine are highly bound to plasma proteins, dialysis is unlikely to result in significant removal of the active substances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR21

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.

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

Pharmacodynamic effects

Antiviral activity in cell culture
The IC_{50} for dolutegravir against various laboratory strains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC_{50}s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC_{50} value was 0.2 nM (range 0.02-2.14). The mean IC_{50} for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median IC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng/mL). Rilpivirine demonstrated limited *in vitro* activity against HIV-2 with IC_{50} values ranging from 2,510 to 10,830 nM.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (clades A, B, C, D, F, G, H) primary isolates with IC_{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.

Effect of human serum and serum proteins
In 100% human serum, the dolutegravir mean protein fold shift was 75 fold, resulting in protein adjusted IC_{90} of 0.064 μg/mL.

A reduction in the antiviral activity of rilpivirine was observed in the presence of 1 mg/mL alpha-1-acid glycoprotein, 45 mg/mL human serum albumin, and 50% human serum as demonstrated by median IC_{50} rates of 1.8, 39.2 and 18.5, respectively.

Resistance

Resistance in vitro
Serial passage is used to study resistance evolution *in vitro*. For dolutegravir, when using the laboratory strain HIV-1 IIIB during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and F; these mutations were not selected in patients treated with dolutegravir in the clinical studies. Using strain NL432, integrase mutations E92Q (fold change [FC] 3) and G193E (FC 3) were selected. These mutations have been selected in patients with pre-existing raltegravir resistance and who were then treated with dolutegravir (listed as secondary mutations for dolutegravir).

In further selection experiments using clinical isolates of subtype B, mutation R263K was seen in all five isolates (after 20 weeks and onwards). In subtype C (n=2) and A/G (n=2) isolates the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two individual patients with subtype B and subtype C in the Phase III clinical program for ART experienced, INI naive

subjects, but without effects on dolutegravir susceptibility *in vitro*. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10), but was not detected in patients receiving dolutegravir in the Phase III program.

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q, T66I) do not affect the *in vitro* susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to primary mutations (excluding at Q148) in experiments with site directed mutants, dolutegravir susceptibility remains at or near wildtype level. In the case of the Q148-mutation viruses, increasing dolutegravir FC is seen as the number of secondary mutations increase. The effect of the Q148-based mutations (H/R/K) was also consistent with *in vitro* passage experiments with site directed mutants. In serial passage with strain NL432-based site directed mutants at N155H or E92Q, no further selection of resistance was seen (FC unchanged around 1). In contrast, starting passage with mutants with mutation Q148H (FC 1), a variety of raltegravir associated secondary mutations accumulated with a consequent increase of FC to values >10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

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
Two subjects across the pooled SWORD-1 (201636) and SWORD-2 (201637) studies from each treatment arm experienced confirmed virologic failure leading to withdrawal at any time through Week 48. NNRTI resistance associated substitution K101K/E mixture with no decreased susceptibility to rilpivirine (FC=1.2) was observed in one subject with identified adherence issues that received dolutegravir plus rilpivirine. No integrase resistance was observed. This patient's viral load was 1,059,771 copies/mL at the suspected virologic withdrawal visit and was <50 copies/mL at the withdrawal visit. No treatment emergent resistance-associated substitutions were observed for the other three subjects who experienced confirmed virologic failure.

In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class, or to the NRTI class was seen (n=876, follow-up of 48-96 weeks).

In patients with prior failed therapies, but naïve to the integrase class (SAILING study), integrase inhibitor substitutions were observed in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase inhibitor experienced or infected with integrase inhibitor resistant virus by transmission. The R263K mutation was also selected *in vitro* (see above).

From rilpivirine Phase III trials, in the week 48 pooled resistance analysis conducted with previously untreated patients, 62 (of a total of 72) virologic failures in the rilpivirine arm had resistance data at baseline and time of failure. In this analysis, the resistance-associated mutations (RAMs) associated with NNRTI resistance that developed in at least 2 rilpivirine virologic failures were: V90I, K101E, E138K, E138Q, V179I, Y181C, V189I, H221Y, and F227C. In the trials, the presence of the mutations V90I and V189I, at baseline, did not affect response. The E138K substitution emerged most frequently during rilpivirine treatment, commonly in combination with the M184I substitution. In the week 48 analysis, 31 out of 62 of rilpivirine virologic failures had concomitant NNRTI and NRTI RAMs; 17 of those 31 had the combination of E138K and M184I. The most common mutations were the same in the week 48 and week 96 analyses. From the week 48 to the week 96 analysis, 24 (3.5%) and 14 (2.1%) additional virologic failures occurred in the rilpivirine and efavirenz arm, respectively.

Cross-resistance

Site-directed INI mutant virus
Dolutegravir activity was determined against a panel of 60 INI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions). The single INI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference).

Site-directed NNRTI mutant virus
In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity (FC≤BCO) against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N substitution did not result in reduced susceptibility to rilpivirine by itself, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine.
Considering all of the available *in vitro* and *in vivo* data, the following amino acid substitutions, when present at baseline, are likely to affect the activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I or M230L.

Recombinant clinical isolates
Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analysed for susceptibility to dolutegravir. Dolutegravir had a <10 FC against 94% of the 705 clinical isolates.

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

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

Effects on electrocardiogram

The effect of rilpivirine at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. Rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg once daily 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 once daily 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 recommended 25 mg once daily dose of rilpivirine (see section 4.4).

No relevant effects were seen with dolutegravir on the QTc interval, with doses exceeding the clinical dose by approximately three fold.

Clinical efficacy and safety

The efficacy and safety of switching from an antiretroviral regimen (containing 2 NRTIs plus either an INI, an NNRTI, or a PI) to a dual regimen of dolutegravir 50 mg and rilpivirine 25 mg was evaluated in 2

identical 48-week, randomised, open-label, multicentre, parallel-group, non-inferiority studies SWORD-1 (201636) and SWORD-2 (201637). Subjects were enrolled if they were on their first or second antiretroviral regimen with no history of virological failure, had no suspected or known resistance to any antiretroviral and had been stably suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months prior to screening. Subjects were randomised 1:1 to continue their CAR or be switched to a two-drug regimen dolutegravir plus rilpivirine administered once daily. The primary efficacy endpoint for the SWORD studies was the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm for the ITT-E population).

At baseline, in the pooled analysis, characteristics were similar between treatment arms with the median age of subjects of 43 years (28%, 50 years of age or older; 3%, 65 years of age or older), 22% female, 20% non-white and 77% were CDC Class A. Median CD+cell count was about 600 cells per mm^3 with 11% having CD4+ cell count less than 350 cells per mm^3. In the pooled analysis, 54%, 26%, and 20% of subjects were receiving an NNRTI, PI, or INI (respectively) as their baseline third treatment agent class prior to randomisation.

The pooled primary analysis demonstrated that dolutegravir plus rilpivirine is non-inferior to CAR, with 95% of subjects in both arms achieving the primary endpoint of <50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm (Table 3).

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

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

	SWORD-1 and SWORD-2 Pooled Data* **	
	DTG + RPV N=513 n (%)	**CAR N=511 n (%)**
HIV-1 RNA <50 copies/mL	486 (95%)	485 (95%)
Treatment Difference*	-0.2 (-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 Third Treatment Agent Class		
INI	99 / 105 (94%)	92 / 97 (95%)
NNRTI	263 / 275 (96%)	265 / 278 (95%)
PI	124 / 133 (93%)	128 / 136 (94%)
Gender		
Male	375 / 393 (95%)	387 / 403 (96%)

Female	111 / 120 (93%)	98 / 108 (91%)
Race		
White	395 / 421 (94%)	380 / 400 (95%)
African-America/African Heritage/Other	91 / 92 (99%)	105 / 111 (95%)
Age (years)		
<50	350 / 366 (96%)	348 / 369 (94%)
≥50	136 / 147 (93%)	137 / 142 (96%)

* Adjusted for baseline stratification factors and assessed using a non-inferiority margin of - 8%.
** Non-inferiority of dolutegravir plus rilpivirine to CAR, in the proportion of subjects classified as virologic non-responders, was demonstrated using a non-inferiority margin of 4%. Adjusted difference (95% CI) -0.6 (-1.7, 0.6).
*** The results of the pooled analysis are in line with those of the individual studies, for which differences in proportions meeting the primary endpoint of <50 copies/mL plasma HIV-1 RNA at Week 48 (based on the Snapshot algorithm) for DTG+RPV versus CAR were -0.6 (95% CI: -4.3; 3.0) for SWORD-1 and 0.2 (95% CI: -3.9; 4.2) for SWORD-2 with a preset non-inferiority margin of -10%.
N = Number of subjects in each treatment arm
CAR = current antiretroviral regimen; DTG+RPV = dolutegravir plus rilpivirine;
INI = Integrase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor;
PI = Protease Inhibitor

Effects on bone
In a DEXA substudy mean bone mineral density (BMD) increased from Baseline to Week 48 in subjects who switched to dolutegravir plus rilpivirine (1.34% total hip and 1.46% lumbar spine) compared with those who continued on treatment with a TDF-containing antiretroviral regimen (0.05% total hip and 0.15% lumbar spine. Any beneficial effect on fracture rate was not studied.

Pregnancy

No efficacy and safety data are available for the combination of dolutegravir and rilpivirine in pregnancy. 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). Of the 12 subjects that completed the study, 10 subjects were suppressed at the end of the study; in the other 2 subjects an increase in viral load was observed postpartum, for 1 subject due to suspected suboptimal adherence. 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. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults.

In limited data from small numbers of women who received dolutegravir 50 mg once daily in combination with a background regimen, the total exposure (AUC) to dolutegravir was 37% lower during the 2nd trimester of pregnancy, and 29% lower during the 3rd trimester of pregnancy, compared with postpartum (6-12 weeks). Of the 29 subjects that completed the study, 27 subjects were suppressed at the end of the study. No mother to child transmission was identified. While 24 infants were confirmed to be uninfected, 5 were indeterminate due to incomplete testing, see sections 4.2, 4.4 and 5.2.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Juluca in one or more subsets of the paediatric population in the treatment of HIV infection.

5.2 Pharmacokinetic properties

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

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. In Phase I studies in healthy subjects, between-subject CVb% for AUC and C_{max} ranged from ~20 to 40% and $C\tau$ from 30 to 65% across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw%) is lower than between-subject variability.

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

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for tablet formulation. After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours.

Juluca must be taken with a meal to obtain optimal absorption of rilpivirine (see section 4.2). When Juluca was taken with a meal, the absorption of both dolutegravir and rilpivirine was increased. Moderate and high fat meals increased the dolutegravir AUC(0-∞) by approximately 87% and C_{max} by approximately 75%. Rilpivirine AUC(0-∞) was increased by 57% and 72% and C_{max} by 89% and 117%, with moderate and high fat meals respectively, compared to fasted conditions. Taking Juluca in fasted condition or with only a protein-rich nutritional drink may result in decreased plasma concentrations of rilpivirine, which could potentially reduce the therapeutic effect of Juluca.

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

Distribution

Dolutegravir is highly bound (>99%) to human plasma proteins based on *in vitro* data. The apparent volume of distribution is 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC_{50}).

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

Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Biotransformation

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low (< 1% of the dose). 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 active substance or biliary

excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine, mainly represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the CYP3A system.

Drug interactions

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50}>50 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see section 4.5).

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Elimination

Dolutegravir has a terminal half-life of ~14 hours. The apparent oral clearance (CL/F) is approximately 1L/hr in HIV-infected patients based on a population pharmacokinetic analysis.

The terminal elimination half-life of rilpivirine is approximately 45 hours. After single dose oral administration of ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.

Special patient populations

Children
Neither Juluca nor the combination dolutegravir and rilpivirine as single entities have been studied in children. Dosing recommendations for paediatric patients cannot be made due to insufficient data (see section 4.2).

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to <18 years of age and weighing ≥40 kg) showed that dolutegravir 50 mg once daily oral dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 mg orally once daily. The pharmacokinetics was evaluated in 11 children 6 to 12 years of age and showed that 25 mg once daily in patients weighing at least 20 kg and 35 mg once daily in patients weighing at least 30 kg resulted in dolutegravir exposure comparable to adults.

The pharmacokinetics of rilpivirine in 36 antiretroviral treatment-naïve HIV-1 infected adolescent subjects (12 to <18 years of age) receiving rilpivirine 25 mg once daily were comparable to those in treatment-naïve HIV-1 infected adults receiving rilpivirine 25 mg once daily. There was no impact of body weight on rilpivirine pharmacokinetics in paediatric subjects in study C213 (33 to 93 kg), similar to what was observed in adults.

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

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr <30 mL/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency.

Renal elimination of rilpivirine is negligible. No dose adjustment is needed for patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, Juluca should be used with caution, as rilpivirine plasma concentrations may be increased due to alteration of drug absorption, distribution and/or metabolism secondary to renal dysfunction. In patients with severe renal impairment or end-stage renal disease, the combination of Juluca with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. Juluca has not been studied in patients on dialysis. As dolutegravir and rilpivirine are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis (see section 4.2).

Hepatic impairment
Dolutegravir and rilpivirine are both primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh score B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5- to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls.

In a rilpivirine study comparing 8 patients with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. However, it may not be excluded that the pharmacologically active, unbound, rilpivirine exposure is significantly increased in moderate hepatic impairment.

No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment (Child-Pugh score A or B). Juluca should be used with caution in patients with moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh score C) on the pharmacokinetics of dolutegravir or rilpivirine has not been studied, therefore Juluca is not recommended in these patients.

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

Race
No clinically important pharmacokinetic differences of dolutegravir or rilpivirine due to race have been identified.

Co-infection with Hepatitis B or C
Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir or rilpivirine. Subjects with hepatitis B co-infection or hepatitis C infection in need of anti-HCV therapy were excluded from studies with the dual combination of dolutegravir and rilpivirine.

Pregnancy and postpartum
No pharmacokinetic data are available for the combination of dolutegravir and rilpivirine in pregnancy. In limited data from small numbers of women in study IMPAACT P1026 who received dolutegravir 50 mg once daily during the 2nd trimester of pregnancy, mean intra-individual values for total dolutegravir C_{max}, AUC_{24h} and C_{24h} values were, respectively, 26%, 37% and 51% lower as compared to postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h} and C_{min} values were, respectively, 25%, 29% and 34% lower as compared to postpartum (see sections 4.2, 4.4. and 4.6).

In women receiving rilpivirine 25 mg once daily during the 2nd trimester of pregnancy, mean intra-individual values for total rilpivirine C_{max}, AUC_{24h} and C_{min} values were, respectively, 21%, 29% and 35% lower as compared to postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h} and C_{min} values were, respectively, 20%, 31% and 42% lower as compared to postpartum (see sections 4.2, 4.4. and 4.6).

5.3 Preclinical safety data

Carcinogenesis and 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 has 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. Carcinogenicity studies with rilpivirine in mice and rats revealed tumorigenic potential specific for these species, but are regarded as of no relevance for humans.

Reproductive toxicology studies

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (33 times the 50 mg human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (38 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 1000 mg/kg (0.56 times the 50 mg human clinical exposure based on AUC).

Rilpivirine studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

Repeated dose toxicity

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 active substance 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 a 50 kg human), and 11 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg.

Liver toxicity associated with liver enzyme induction was observed in rodents following rilpivirine administration. In dogs, cholestasis-like effects were noted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)
Magnesium stearate
Microcrystalline cellulose
Povidone (K29/32)
Sodium starch glycolate
Sodium stearyl fumarate
Lactose monohydrate
Croscarmellose sodium
Povidone (K30)
Polysorbate 20
Silicified microcrystalline cellulose

Tablet coating

Polyvinyl alcohol- part hydrolysed
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

White HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures, with a polyethylene faced induction heat seal liner. Each pack consists of one bottle containing 30 film-coated tablets and a desiccant.

Multipacks containing 90 (3 packs of 30) film-coated tablets. Each pack of 30 film-coated tablets contains a desiccant.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1282/001
EU/1/18/1282/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 May 2018

10. DATE OF REVISION OF THE TEXT

29 November 2018

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.