1. NAME OF THE MEDICINAL PRODUCT

Juluca

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

Dolutegravir/rilpivirine should be prescribed by physicians experienced in the management of HIV infection.

Posology

The recommended dose of Juluca is one tablet once daily. The tablet 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 Physician leaflets for these medicinal products.

Missed doses
If the patient misses a dose of Juluca, the patient should take the missed dose 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 dolutegravir/rilpivirine, another dolutegravir/rilpivirine tablet should be taken with a meal. If a patient vomits more than 4 hours after taking dolutegravir/rilpivirine, the patient does not need to take another dose of dolutegravir/rilpivirine 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 dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). Dolutegravir/rilpivirine 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 dolutegravir/rilpivirine 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.

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:
- fampridine (also known as dalfampridine);
- 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

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. dolutegravir/rilpivirine 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 dolutegravir/rilpivirine after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids and weight, there is in some cases evidence for a treatment effect. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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. Dolutegravir/rilpivirine 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 dolutegravir/rilpivirine 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

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

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).

H_2-receptor antagonists
Dolutegravir/rilpivirine 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 dolutegravir/rilpivirine (see section 4.5).

Antacids
Dolutegravir/rilpivirine 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 dolutegravir/rilpivirine (see section 4.5).

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

Metformin
Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir/rilpivirine 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 dolutegravir/rilpivirine. 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.

Immune Reconstitution 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 medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 dolutegravir/rilpivirine 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 dolutegravir/rilpivirine with medicinal products that induce CYP3A may result in decreased plasma concentrations of rilpivirine, which

could reduce the therapeutic effect of dolutegravir/rilpivirine (see Table 1). Co-administration of dolutegravir/rilpivirine with medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine (see Table 1). In patients with severe renal impairment or end stage renal disease, the combination of dolutegravir/rilpivirine with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk (see section 4.2).

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

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 MATE1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 and/or MATE1 (e.g. fampridine [also known as dalfampridine], 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}", minimum observed concentration as "C_{min}"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%	No dose adjustment is required.

Tenofovir disoproxil / Rilpivirine[1,2]	Cτ ↓ 8% Tenofovir ↔ Rilpivirine AUC ↔ C_{min} ↔ C_{max} ↔ Tenofovir AUC ↑ 23% C_{min} ↑ 24% C_{max} ↑ 19%	
Tenofovir alafenamide / Dolutegravir Tenofovir alafenamide / Rilpivirine[1]	Dolutegravir ↔ (Not studied) Rilpivirine ↔	No dose adjustment is required.
Lamivudine/ Dolutegravir Lamivudine/ Rilpivirine	Dolutegravir ↔ Rilpivirine ↔ (Not studied)	No dose adjustment is required.
Entecavir/ Dolutegravir Entecavir/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ (Not studied)	No dose adjustment is required.
Daclatasvir/ Dolutegravir[1] Daclatasvir/ Rilpivirine	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔ Rilpivirine ↔	No dose adjustment is required.
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 ↔	No dose adjustment is required.

	C_{min} ↔ C_{max} ↔ Sofosbuvir ↔ AUC ↔ C_{max} ↑ 21% Sofosbuvir metabolite GS-331007 ↔ AUC ↔ C_{max} ↔	
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} ↔ Sofosbuvir metabolite GS-331007 ↔ AUC ↔ C_{min} ↔ C_{max} ↔ Velpatasvir ↔ AUC ↔ C_{min} ↔ C_{max} ↔	No dose adjustment is required.
Ribavirin/ Dolutegravir Ribavirin/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ (Not studied)	No dose adjustment is required.
Other active substances		
Antiarrhythmics		

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 dolutegravir/rilpivirine 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 (induction of CYP3A enzymes).	Metabolic inducers may significantly decrease dolutegravir/rilpivirine plasma concentrations, resulting in loss of therapeutic effect. Co-administration of dolutegravir/rilpivirine with these metabolic inducers is contraindicated (see section 4.3).
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	Dolutegravir ↔ (Not studied)	No dose adjustment is required.
Fluconazole Itraconazole Isavuconazole Posaconazole Voriconazole/ Rilpivirine	Rilpivirine ↑ Not studied. May cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes).	
Herbal products		
St. John's wort/ Dolutegravir	Dolutegravir ↓ Not studied. Decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected.	Co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of dolutegravir/rilpivirine. Co-administration of dolutegravir/rilpivirine with St. John's wort is contraindicated (see section 4.3).
St. John's wort/ Rilpivirine	Rilpivirine ↓ Not studied. Significant decreases in rilpivirine plasma concentrations are expected (induction of CYP3A enzymes).	
Potassium channel blockers		
Fampridine (also known as dalfampridine)/ Dolutegravir	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with dolutegravir/rilpivirine is contraindicated (see section 4.3).
Proton pump inhibitors		
Omeprazole Lansoprazole Rabeprazole Pantoprazole Esomeprazole/ Dolutegravir	Dolutegravir ↔ (Not studied)	Co-administration may significantly decrease rilpivirine plasma concentration. This may result in loss of therapeutic effect of dolutegravir/rilpivirine. Co-administration of dolutegravir/rilpivirine 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 dolutegravir/rilpivirine 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 dolutegravir/rilpivirine (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]	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% C_{24} ↓ 74% (Complex binding to polyvalent ions). Rilpivirine ↓	The combination of dolutegravir/rilpivirine and antacids should be used with particular caution. Antacids should be taken well separated in time from the administration of dolutegravir/rilpivirine (minimum 6 hours before or 4 hours after).

Antacids (e.g., aluminium magnesium hydroxide, and/or calcium carbonate)/ Rilpivirine	Not studied. Significant decreases in rilpivirine plasma concentrations are expected (reduced absorption due to gastric pH increase).	
Calcium supplements/ Dolutegravir[1]	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions).	The combination of dolutegravir/rilpivirine and supplements should be used with particular caution. Calcium supplements, iron supplements or multivitamins should be co-administered at the same time as dolutegravir/rilpivirine with a meal. If calcium supplements, iron supplements or multivitamins cannot be taken at the same time as dolutegravir/rilpivirine, these supplements should be taken well separated in time from the administration of dolutegravir/rilpivirine (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]	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% Cτ ↑ 17%	No dose adjustment is required.
Prednisone/ Rilpivirine	Rilpivirine ↔ (Not studied)	
Dexamethasone/ Dolutegravir	Dolutegravir ↔ (Not studied)	Co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of dolutegravir/rilpivirine. Co-administration of dolutegravir/rilpivirine with systemic dexamethasone is contraindicated (except as a single dose) see section 4.3. Alternatives should be considered, particularly for long-term use.
Dexamethasone/ Rilpivirine (systemic, except for single dose use)	Rilpivirine ↓ Not studied. Dose dependent decreases in rilpivirine plasma concentrations are expected (induction of CYP3A enzymes).	
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 dolutegravir/rilpivirine 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] Rifampicin/ Rilpivirine[1,2]	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓72% (induction of UGT1A1 and CYP3A enzymes). 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} ↔	Co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of dolutegravir/rilpivirine. Co-administration of dolutegravir/rilpivirine with rifampicin is contraindicated (see section 4.3).
Rifabutin/ Dolutegravir[1] Rifabutin/ Rilpivirine[1] 300 mg once daily[2] 300 mg once daily (+ 25 mg once daily rilpivirine) 300 mg once daily (+ 50 mg once daily rilpivirine)	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes). Rifabutin AUC ↔ C_{min} ↔ C_{max} ↔ 25-*O*-desacetyl-rifabutin AUC ↔ C_{min} ↔ C_{max} ↔ Rilpivirine AUC ↓ 42% C_{min} ↓ 48% C_{max} ↓ 31% Rilpivirine AUC ↑ 16%* C_{min} ↔* C_{max} ↑ 43%* * compared to 25 mg once daily rilpivirine alone (induction of 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).
Rifapentine/ Dolutegravir	Dolutegravir ↓ (Not studied)	Co-administration may cause significant decreases in rilpivirine plasma concentrations. This may

Rifapentine/ Rilpivirine	Rilpivirine ↓ Not studied. Significant decreases in rilpivirine plasma concentrations are expected.	result in loss of therapeutic effect of dolutegravir/rilpivirine (induction of CYP3A enzymes). Co-administration of dolutegravir/rilpivirine 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 dolutegravir/rilpivirine 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 Ethinyl estradiol (EE)[1] and Norethindrone[1]/ Rilpivirine	Dolutegravir ↔ EE ↔ AUC ↑ 3% C_{max} ↓ 1% NGMN ↔ AUC ↓ 2% C_{max} ↓ 11% Rilpivirine ↔* EE ↔ AUC ↔ C_{min} ↔ C_{max} ↑ 17% Norethindrone ↔ AUC ↔ C_{min} ↔	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.

	C_{max} ↔ *based on historic controls.	
Analgesics		
Methadone/ Dolutegravir[1] Methadone / Rilpivirine[1]	Dolutegravir ↔ Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% Cτ ↓ 1% Rilpivirine: AUC: ↔* C_{min}: ↔* C_{max}: ↔* R(-) methadone: AUC: ↓ 16% C_{min}: ↓ 22% C_{max}: ↓ 14% *based on historic controls.	No dose adjustments are required when initiating co-administration of methadone with dolutegravir/rilpivirine. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Paracetamol/ Dolutegravir Paracetamol / Rilpivirine[1,2]	Dolutegravir ↔ (Not studied) Rilpivirine AUC ↔ C_{min} ↑ 26% C_{max} ↔ Paracetamol AUC ↔ C_{min} NA C_{max} ↔	No dose adjustment is required.
Anticoagulants		
Dabigatran etexilate/ Dolutegravir Dabigatran etexilate/ Rilpivirine	Dolutegravir ↔ (Not studied) Rilpivirine ↔ Not studied. Dabigatran etexilate ↑ A risk for increases in dabigatran plasma concentrations cannot be excluded (inhibition of intestinal P-gp).	The combination of dolutegravir/rilpivirine and dabigatran etexilate should be used with caution.
HMG CO-A reductase inhibitors		
Atorvastatin/ Dolutegravir Atorvastatin/ Rilpivirine[1,2]	Dolutegravir ↔ (Not studied) Rilpivirine AUC ↔ C_{min} ↔ C_{max} ↓ 9%	No dose adjustment is required.

	Atorvastatin AUC ↔ C_{min} ↓ 15% C_{max} ↑ 35%	
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 medicinal product.

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). Dolutegravir/rilpivirine 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

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (a component of Juluca, see below), including consideration of effective contraceptive measures.

If a woman plans pregnancy, the benefits and the risks of continuing treatment with Juluca should be discussed with the patient.

Pregnancy

Lower exposures of dolutegravir and rilpivirine were observed during pregnancy (see sections 5.1, 5.2). In phase 3 studies, lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure. The use of Juluca during pregnancy is not recommended.

The safety and efficacy of a dual regimen has not been studied in pregnancy.

Human experience from a birth outcome surveillance study in Botswana shows a small increase of neural tube defects; 7 cases in 3,591 deliveries (0.19%; 95% CI 0.09%, 0.40%) to mothers taking dolutegravir-containing regimens at the time of conception compared to 21 cases in 19,361 deliveries (0.11%: 95% CI 0.07%, 0.17%) to women exposed to non-dolutegravir regimens at the time of conception.

The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births (0.05-0.1%). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

Data analysed from the Antiretroviral Pregnancy Registry do not indicate an increased risk of major birth defects in over 600 women exposed to dolutegravir during pregnancy but are currently insufficient to address the risk of neural tube defects.

In animal reproductive toxicology studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified (see section 5.3).

More than 1000 outcomes from exposure to dolutegravir during second and third trimester pregnancy indicate no evidence of increased risk of foetal/neonatal toxicity.

Dolutegravir crosses the placenta in humans. In pregnant women living with HIV, the median foetal umbilical cord concentration of dolutegravir was approximately 1.3-fold greater compared with the maternal peripheral plasma concentration.

There is insufficient information on the effects of dolutegravir on neonates.

Animal studies with rilpivirine do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Breast-feeding

It is unknown if rilpivirine is excreted in human milk. Available toxicological data in animals has shown excretion of rilpivirine in milk. Dolutegravir is excreted in human milk in small amounts (a median dolutegravir breast milk to maternal plasma ratio of 0.033 has been shown). There is insufficent information on the effects of dolutegravir in newborns/infants.

It is recommended that women living with HIV do not breast-feed their infants 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

Juluca has no or negligible influence on the 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

The most frequently reported adverse reactions with Juluca (from clinical studies – see section 5.1) were diarrhoea (2%) and headache (2%).

The most severe adverse reaction, related to the treatment with dolutegravir (from pooled 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 sources of information for the safety database include 2 identical, randomised, open-label studies SWORD-1 and SWORD-2 (see section 5.1), pooled studies from individual components and post-marketing experience.

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 list 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), panic attack
	rare	completed suicide (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, weight increased
* 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 or rilpivirine have been associated with increases in serum creatinine occurring 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 dolutegravir/rilpivirine and remained stable through 148 weeks. A mean change from baseline of 9.86 μmol/L (SD 10.4 μmol/L) was observed after 148 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.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

Additionally, you should also report to GSK Israel (il.safety@gsk.com)

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 dolutegravir/rilpivirine. 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
Through 48 Weeks with comparative data two subjects receiving dolutegravir plus rilpivirine and two subjects continuing their current antiretroviral regimen (CAR) experienced confirmed virologic failure leading to withdrawal (CVW) criteria across the pooled SWORD-1 (201636) and SWORD-2 (201637) studies. Overall eleven subjects receiving dolutegravir plus rilpivirine met CVW through Week 148, see Table 3. The NNRTI-associated substitutions E138E/A and M230M/L were detected in three and two subjects at time of withdrawal.

Table 3: Summary of resistance by drug class for subjects with confirmed virologic withdrawal in early and late switch phases of the SWORD studies

Regimen / Treatment exposure **(weeks)***	**HIV-1 RNA (c/mL) (time point)**		**Mutation by Drug Class mutation (FC)*** **			
			INI		**NNRTI**	
	SVW	**CVW****	**BL**	**VW**	**BL**	**VW**
DTG+RPV / 36	88 (Wk24)	466 (Wk24UNS)	G193E	G193E (1.02)	none	none
DTG+RPV / 47	1,059,771 (Wk36)	1018 (Wk36UNS)	none	none	none	K101K/E (0.75)
DTG+RPV / 21	162 (Wk64)	217 (Wk76)	L74I	NR	V108I	NR
DTG+RPV / 17	833 (Wk64)	1174 (Wk64UNS)	N155N/H G163G/R	V151V/I (NR)	none	none
DTG+RPV / 88	278 (Wk76)	2571 (Wk88)	none	none	none	E138E/A (1.61)
DTG+RPV / 92	147 (Wk88)	289 (Wk88UNS)	ND	none	NR	K103N (5.24)
DTG+RPV / 105	280 (Wk88)	225 (Wk100)	none	none	none	none
DTG+RPV / 105	651 (Wk100)	1105 (Wk100UNS)	G193E	NR	K101E, E138A	K101E, E138A, M230M/L (31)
DTG+RPV / 120	118 (Wk112)	230 (Wk112UNS)	E157Q G193E, T97T/A	E157Q, G193E (1.47)	none	M230M/L (2)
DTG+RPV / 101	4294 (Wk136)	7247 (Wk136UNS)	NR	NR	NR	E138A, L100L/I (4.14)

* The resistance testing at virologic failure time failed for one subject, therefore, details are not included in this table.
** CVW was met with 2 consecutive viral loads after Day 1 ≥50 c/mL, with the second one being >200 c/mL.
*** The baseline assay only provides genotypic data, and not phenotypic data.

CAR = current antiretroviral regimen; DTG+RPV = dolutegravir plus rilpivirine
SVW = suspected virologic withdrawal criteria; CVW = confirmatory virologic withdrawal criteria; BL = baseline resistance testing results; VW = resistance testing results when CVW criteria have been met; Wk = week; UNS = unscheduled visit; “ND” Baseline testing was not performed as PBMC/Whole blood samples were note collected; “none” indicates no resistance observed; "NR" indicates data are not reported due to assay failure or sample unavailability.

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 IIIstudies, 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 studies, 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 148-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-agent 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 4).

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 4.

Table 4: Virologic outcomes of randomised 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 agent due to adverse event or death	17 (3%)	3 (<1%)
Discontinued study/study agent 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

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

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 study 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 study 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 section 5.2.

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 metabolised 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

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, dolutegravir/rilpivirine 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 dolutegravir/rilpivirine with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. Dolutegravir/rilpivirine 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 metabolised 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 dose adjustment is considered necessary for patients with mild to moderate hepatic impairment (Child-Pugh score A or B). Dolutegravir/rilpivirine 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 dolutegravir/rilpivirine 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 section 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 section 4.6).

5.3 Preclinical safety data

Non-clinical data for dolutegravir and rilpivirine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. While dolutegravir was not carcinogenic in long-term animal studies, rilpivirine caused an increase in hepatocellular neoplasms in mice that may be species specific.

Reproductive toxicology studies

In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta.

Dolutegravir did not affect male or female fertility in rats at 33 times higher exposures than the AUC-exposure at 50 mg human clinical dose.

Oral administration of dolutegravir to pregnant rats 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 did not elicit developmental toxicity or teratogenicity (0.56 times the 50 mg human clinical exposure based on AUC).

Rilpivirine studies in rats and rabbits have shown no teratogenicity and no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function at exposures respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

The
Liver

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Microcrystalline cellulose
Lactose monohydrate
Silicified microcrystalline cellulose

Sodium starch glycolate (Type A)
Povidone K29/32
Sodium stearyl fumarate
Povidone K30
Magnesium stearate
Croscarmellose sodium
Polysorbate 20

Tablet coating (Opadry II Pink 85F240164)

Polyvinyl alcohol
Titanium dioxide
Macrogol/PEG
Talc
Yellow Iron oxide

Red Iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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.

Store below 30ºC.

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.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MANUFACTURER

Glaxo Welcome S.A.
Avda. Extremadura 3, 09400 Aranda De Duero, Burgos, Spain.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

161-69-35445-00

Revised in April 2023 according to MOHs guidelines

Jul tab DR v11