ABRIDGED SUMMARY OF THE CHARACTERISTICS OF THE PRODUCT

Please refer to the Summary of Product Characteristics for a complete information on the use of this product.

BT_1000x858pxThis 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 “Undesirable effects” for how to report adverse reactions.

**NAME OF THE MEDICINAL PRODUCT**

Juluca 50 mg/25 mg film-coated tablets- EU/1/18/1282/001

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

**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).

**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.

**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.

Separate preparations of dolutegravir or rilpivirine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. 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.

*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.

*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.

*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 of the complete SmPC, 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 section “Special warnings and precautions for use”).

Method of administration

Oral use

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

**Contraindications**

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

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*).

**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.

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, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. 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) . 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 .

Juluca should not be co-administered at the same time as H2-receptor antagonists. These medicinal products are recommended to be administered 12 hours before or 4 hours after Juluca .

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.

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.

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. 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.

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.

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.

**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 “Special warnings and precautions for use”).

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 (see section “Special warnings and precautions for use”) |
| 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 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 Juluca and remained stable through 148 weeks. A mean change from baseline of 9.86 mol/L (SD 10.4 mol/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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

|  |  |
| --- | --- |
| **Belgium**  Federal Agency for Medicines and Health Products  Division Vigilance  Boîte Postale 97  B-1000 Brussels  Madou  Website: [www.notifieruneffetindesirable.be](http://www.notifieruneffetindesirable.be)  e-mail: [adr@afmps.be](mailto:adr@afmps.be) | **Luxembourg**  Centre Régional de Pharmacovigilance de Nancy  Bâtiment de Biologie Moléculaire et de Biopathologie (BBB)  CHRU de Nancy – Hôpitaux de Brabois  Rue du Morvan  54 511 Vandoeuvre Les Nancy Cedex  Tél : (+33) 3 83 65 60 85 / 87  e-mail : [crpv@chru-nancy.fr](mailto:crpv@chru-nancy.fr)  ou  Direction de la Santé  Division de la Pharmacie et des Médicaments  20, rue de Bitbourg  L-1273 Luxembourg-Hamm  Tél.: (+352) 2478 5592  e-mail: pharmacovigilance@ms.etat.lu  Link pour le formulaire : <https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.html> |

**MARKETING AUTHORISATION HOLDER**

ViiV Healthcare BV, Van Asch van Wijckstraat 55H, 3811 LP Amersfoort, Netherlands

**DATE OF APPROVAL OF THE TEXT**

08/2021 (v09)

**DELIVERY STATUS**

Medicinal product subject to medical prescription.