

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a physician's prescription only

JULUCA

Film-Coated Tablets.

Each tablet contains:

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

For the list of inactive and allergenic ingredients in the preparation, see section 2 - "Important information about some of the ingredients of the medicine" and section 6 - "Further information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the physician or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Juluca is used to treat HIV in adults aged 18 and above who are being treated with antiretroviral medicines and whose HIV-1 infection is under control for at least 6 months, with no history of virological failure and no known or suspected resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or integrase inhibitors.

Juluca keeps the amount of HIV virus in your body at a low level. This helps maintain the number of CD4 cells in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.

Therapeutic group

Juluca is a medicine that contains two active ingredients used to treat HIV infection: dolutegravir and rilpivirine. Dolutegravir belongs to a group of antiretroviral medicines called *integrase inhibitors (INIs)*. Rilpivirine belongs to a group of antiretroviral medicines called *non-nucleoside reverse transcriptase inhibitors (NNRTIs)*.

2. BEFORE USING THE MEDICINE

Do not use the medicine:

- if you are sensitive (allergic) to the active ingredients dolutegravir or rilpivirine, or to any of the additional ingredients contained in the medicine (detailed in section 6).
 - if you are taking any of the following medicines, because they may affect the way Juluca works:
 - Fampridine (also known as dalfampridine, used to treat multiple sclerosis)
 - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin (medicines to treat epilepsy and to prevent fits)
 - Rifampicin, rifapentine (medicines to treat some bacterial infections such as tuberculosis)
 - Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole (medicines to prevent and treat stomach ulcers, heartburn or acid reflux disease)
 - Dexamethasone (a corticosteroid used to treat many conditions such as inflammations and allergic reactions) when taken by mouth or injected, except as a single dose treatment
 - Preparations that contain St. John's wort (*Hypericum perforatum*) (a herbal product used for the treatment of depression)
- If you are taking any of the above-mentioned preparations, ask your physician about alternatives.
Tell your physician if you think any of these may apply to you.

Special warnings regarding use of the medicine

Consult with your physician or pharmacist before taking Juluca.

Allergic reactions

Juluca contains dolutegravir. Dolutegravir can cause a serious allergic reaction known as a hypersensitivity reaction. You need to know about important signs and symptoms to look out for while you are taking Juluca. → **Read the information "Allergic reactions" in section 4 of this leaflet.**

Liver problems including hepatitis B and/or C

Tell your physician if you have or have had **Common with your liver**, including hepatitis B and/or C. Your physician will evaluate how severe your liver disease is before deciding if you can take Juluca.

Look out for important symptoms

Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:

- Symptoms of infections and inflammation
 - Joint pain, stiffness and bone problems
- You need to know about important signs and symptoms to look out for while you are taking Juluca. → **Read the information "Other possible side effects" in section 4 of this leaflet.**

Protect other people

HIV infection is spread by sexual contact with someone who is a carrier of the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Talk with your physician about the precautions needed to avoid infecting other people.

Children and adolescents

This medicine is not intended for use in children and adolescents below the age of 18, because it has not been tested in these patients.

Drug interactions

If you are taking, or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the physician or pharmacist.

Juluca must not be taken together with certain other medicines (see "Do not use the medicine if" in section 2).

Some medicines can affect how Juluca works, or make it more likely that you will experience side effects. Juluca can also affect how other medicines work.

Tell your physician if you are taking any of the medicines *from the following list*:

- Metformin, to treat **diabetes**.
- Medicines that may cause a life-threatening irregular heartbeat (*Torsade de Pointes*). As a number of different medicines can cause this condition, you should consult with your physician or pharmacist if you are not sure.
- Medicines called **antacids**, to treat **indigestion and heartburn**. Do not take an antacid during the 6 hours before you take Juluca, or for at least 4 hours after you take it (*see also section 3, "How should you use the medicine"*).
- Calcium supplements, iron supplements and multivitamins** must be taken at the same time as Juluca, with a meal. If you can not take the above mentioned supplements at the same time as Juluca, **do not take a calcium supplement, iron supplement or multivitamins during the 6 hours before you take Juluca, or for at least 4 hours after you take it** (*see also section 3, "How should you use the medicine"*).
- Medicines called H_2 receptor antagonists (for example: cimetidine, famotidine, nizatidine, ranitidine) given to treat **stomach or intestinal ulcers or to relieve heartburn or acid reflux**. Do not take these medicines during the 12 hours before you take Juluca, or for at least 4 hours after taking Juluca (*see also section 3, "How should you use the medicine"*).
- Any other medicine used to treat **HIV infection**.
- Rifabutin, to treat tuberculosis (TB) and other **bacterial infections**. If you take rifabutin, your physician may need to give you an additional dose of rilpivirine in order to treat the HIV infection (*see section 3, "How should you use the medicine"*).
- Artemether/lumefantrine, medicines that prevent you from catching **malaria**.
- Clarithromycin and erythromycin, medicines to treat **bacterial infections**.
- Methadone, a medicine used to treat opiate addiction.
- Dabigatran etexilate, medicines used to treat or prevent **blood clots**.

→ **Tell your physician** if you are taking any of these medicines. Your physician may decide that you need additional tests.

Pregnancy and breast-feeding

Pregnancy

If you are pregnant, think you may be pregnant, or if you are planning to become pregnant:

→ **Use of Juluca is not recommended. Ask your physician for advice.**

Taking Juluca at the time of becoming pregnant or during the first 6 weeks of pregnancy may also increase the risk of a type of birth defect called neural tube defect, such as spina bifida (malformed spinal cord).

If you could get pregnant while taking Juluca:

→ **Talk to your physician** and discuss whether there is a need for contraception, such as condom or pills.

Inform the physician immediately if you become pregnant or if you are planning to become pregnant. Your physician will review your treatment. Do not stop taking Juluca without consulting with your physician, as this may harm you and your unborn child.

Breast-feeding

Women who are HIV carriers must not breast-feed because HIV infection can be passed on to the baby in breast milk.

A small amount of dolutegravir, one of the ingredients in Juluca, can pass into your breast milk. It is not known whether the other ingredient, rilpivirine, can pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding:

→ **Refer to your physician immediately.**

Driving and using machines

Juluca can make you dizzy, tired, sleepy, or cause other side effects that make you less alert.

→ Do not drive or operate machinery unless you are sure you are not affected.

Important information about some of the ingredients of the medicine:

Juluca contains lactose

If you have been told by your physician that you have an intolerance to certain sugars, speak with your physician before taking this medicine.

The medicine contains less than 1 mmol of sodium (23 mg) per dosage unit; it is therefore essentially sodium-free.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use according to the physician's instructions. Check with the physician or pharmacist if you are uncertain.

The dosage and treatment regimen will be determined by your physician.

The usual dosage is generally:

The recommended dosage of Juluca is **one tablet once a day**. Juluca must be taken **with a meal**. A meal is important in order to get the right levels of medicine in your body. A protein drink (a drink rich in protein) alone does not replace a meal.

Do not crush/halve/chew the tablet, in order to ensure the full dose is taken.

Do not exceed the recommended dosage

Rifabutin:

Rifabutin is a medicine to treat some bacterial infections. This medicine can lower the amount of Juluca in your body and make it less effective. If you take rifabutin, the physician may give you an additional dose of rilpivirine. Take the rilpivirine tablet at the same time as Juluca.

→ Consult with your physician about taking rifabutin together with Juluca.

Antacid medicines

Antacids, to treat indigestion and heartburn, can prevent Juluca being absorbed into your body and make it less effective. Do not take an antacid during the 6 hours before you take Juluca, or for at least 4 hours after you take it.

→ Refer to your physician for further advice on taking acid-lowering medicines with Juluca.

Calcium supplements, iron supplements and multivitamins

Calcium supplements, iron supplements or multivitamins can prevent Juluca being absorbed into your body and make it less effective. Calcium supplements, iron supplements or multivitamins must be taken at the same time as Juluca, together with a meal.

If you can not take these supplements at the same time as Juluca, do not take calcium supplements, iron supplements or multivitamins during the 6 hours before you take Juluca, or for at least 4 hours after you take it.

→ Refer to your physician for further advice on taking calcium supplements, iron supplements or multivitamins with Juluca.

H_2 receptor antagonists (for example: cimetidine, famotidine, nizatidine, ranitidine)

H_2 receptor antagonist medicines can prevent Juluca being absorbed into your body and make it less effective.

Do not take these medicines during the 12 hours before taking Juluca, or for at least 4 hours after you take it.

→ Refer to your physician for further advice on taking these medicines with Juluca.

If you accidentally take too high a dosage

If you accidentally take too many tablets of Juluca, **contact your physician or pharmacist immediately**. If possible, show them the Juluca package.

If a child has accidentally swallowed the medicine, refer immediately to a physician or proceed to a hospital emergency room, and bring the package of the medicine with you.

If you forget to take the medicine

If you notice within 12 hours of the time you usually take Juluca, take the tablet as soon as you remember. The Juluca tablet must be taken with a meal. After that, continue your treatment as usual.

If you notice after 12 hours, skip the dose you missed and take the next dose at the usual time.

→ **Do not take a double dose** to make up for a missed dose.

If you vomit less than 4 hours after taking Juluca, take another tablet with a meal. If you vomit more than 4 hours after taking Juluca, you do not need to take another tablet until your next scheduled dose.

Do not stop taking Juluca without consulting your physician

Take Juluca for as long as your physician recommends. Do not stop unless your physician advises you to.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the physician or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Juluca may cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not suffer from any of them.

It is very important to inform your physician about any change in your health.

Allergic reactions

Juluca contains dolutegravir. Dolutegravir can cause a serious allergic reaction known as a hypersensitivity reaction. This is an uncommon (may appear in up to 1 in 100 people) reaction in people taking dolutegravir. If you get any of the following symptoms:

- Skin rash
- A high temperature (fever)
- Lack of energy (*fatigue*)
- Swelling, sometimes of the mouth or face (*angioedema*), causing difficulty in breathing
- Muscle or joint aches

→ **Refer to a physician straight away.** Your physician may decide to carry out tests of your liver, kidneys or blood, and may instruct you to stop taking Juluca.

Very common side effects

These may appear in **more than 1 in 10 people**:

- Headache
- Dizziness
- Diarrhoea
- Nausea
- Difficulties in sleeping (insomnia).

Very common side effects that may show up in blood tests:

- Increase in the levels of liver enzymes (aminotransferase)
- Increase in cholesterol
- Increase in pancreatic amylase enzyme (a digestive enzyme)

Common side effects

These may appear in **up to 1 in 10 people**:

- Loss of appetite
- Rash
- Itching
- Vomiting
- Stomach ache (*upper abdominal pain*) or discomfort
- Wind (*flatulence*)
- Sleepiness
- Sleep disorders
- Abnormal dreams
- Lack of energy (*fatigue*)
- Depression (feelings of deep sadness and lack of self-worth)
- Depressed mood
- Anxiety
- Dry mouth

Common side effects that may show up in blood tests:

- Increase in the level of enzymes produced in the muscles (creatine phosphokinase)
- Decreased number of platelets, blood cells that are involved in the process of blood clotting
- Low white blood cell count
- Decrease in haemoglobin
- Increase in triglycerides (a type of fat)
- Increase in the enzyme lipase (an enzyme involved in breaking down fats)
- Increase in bilirubin (a test of liver function) in the blood

Uncommon side effects

These may appear in **up to 1 in 100 people**:

- Allergic reaction (*hypersensitivity*) (see "allergic reactions" earlier in this section)
- Inflammation of the liver (*hepatitis*)
- Suicidal thoughts and behaviours (particularly in patients who have had depression or mental health problems in the past)
- Panic attack
- Joint pain
- Muscle pain

Rare side effects

These may appear in **up to 1 in 1,000 people**:

- Liver failure (signs may include: yellowing of the skin and the whites of the eyes or unusually dark urine)
 - Suicide (particularly in patients who have had depression or mental health problems before)
- **Tell your physician immediately** if you experience any mental health problems (see also other mental health problems above).

Side effects of unknown frequency

Frequency of the side effect cannot be estimated from the available data:

- Signs and symptoms of inflammation or infection, for example: fever, chills, sweating (*immune reactivation syndrome*)

Other possible side effects

People taking combination therapy for HIV may develop other side effects.

Symptoms of infection and inflammation

People with advanced HIV infection (AIDS) have a weak immune system, and are more likely to develop serious infections (*opportunistic infections*). Symptoms of infection may develop, as a result of old, "hidden" infections flaring up again as the body starts to fight them. The symptoms usually include **fever**, plus some of the following:

- Headache
 - Stomach ache
 - Breathing difficulties
- In rare cases, as the immune system becomes stronger, it can also attack healthy body tissue (*autoimmune disorders*). The symptoms of autoimmune disorders may develop many months after you started taking medicine to treat your HIV infection. The symptoms may include:

- Palpitations (rapid or irregular heartbeat) or tremor
- Hyperactivity (excessive restlessness and movement)
- Weakness beginning in the hands and feet and moving up towards the trunk of the body

If you develop any symptoms of infection or if you notice any of the symptoms above:

→ **Refer to your physician immediately.** Do not take other medicines for the infection without your physician's advice.

Joint pain, stiffness and bone problems

Some of the people taking combination therapy for HIV develop a condition called *osteonecrosis* (bone necrosis). In this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to develop this condition:

- If they have been taking combination therapy for a long time
- If they are also taking anti-inflammatory medicines called corticosteroids
- If they drink alcohol
- If their immune system is very weak
- If they are overweight

Signs of osteonecrosis include:

- Stiffness in the joints
- Aches and pains in the joints (especially in the hip, knee or shoulder)
- Difficulty moving

If you notice any of these symptoms:

→ **Tell your physician.**

Weight, blood lipids and blood glucose effects

During HIV therapy, there may be an increase in weight and in levels of blood lipids and glucose. These effects are partly linked to restored health and lifestyle, and in the case of blood lipids, sometimes to the HIV medicines themselves. Your physician will test for these changes.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in the leaflet, consult with the physician.

Reporting of side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:

<https://sideeffects.health.gov.il>

5. HOW SHOULD THE MEDICINE BE STORED?

• Avoid poisoning! This medicine, and any other medicine, should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the physician.

• Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

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

• Store below 30°C.

• Do not throw away medicines via wastewater or household waste. Consult with the pharmacist on how to throw away medicines that are not in use. These measures will help protect the environment.

6. FURTHER INFORMATION

• In addition to the active ingredients, the medicine also contains -

See also section 2 in the leaflet - "Important information about some of the ingredients of the medicine".

mannitol, microcrystalline cellulose, lactose monohydrate, silicified microcrystalline cellulose, sodium starch glycolate (type A), povidone K30, magnesium stearate, croscarmellose sodium, polyvinyl alcohol, titanium dioxide, macrogol/PEG, talc, yellow iron oxide, red iron oxide.

• What the medicine looks like and the contents of the package -

Juluca film-coated tablets, one oval, biconvex and debossed with "SV J3T" on one side.

The film-coated tablets are provided in a bottle closed with a child-resistant cap.

Directions for opening: In order to remove the cap, press down, while turning it to the left at the same time (counterclockwise).

Directions for closing: Close the bottle well with the cap; turn it to the right (clockwise) until it is completely closed.

Each bottle contains 30 film-coated tablets and a desiccant to reduce moisture. The desiccant should be kept inside the bottle after opening it, do not remove it.

• License Holder: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

• Manufacturer: Glaxo Wellcome, S.A., Burgos, Spain.

• Registration number of the medicine in the National Drug Registry of the Ministry of Health: 161-69-35445-00.

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