Juluca

FACT SHEET

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Summary

Juluca contains two medicines—dolutegravir and rilpivirine. Dolutegravir belongs to the class of drugs called integrase inhibitors. Rilpivirine belongs to the class of drugs called non-nucleoside reverse transcriptase inhibitors ("non-nukes"). Both medicines in Juluca are used for the treatment of HIV. Juluca is taken at a dose of one pill once daily with a meal. Overall, Juluca was well-tolerated in clinical trials. General side effects were uncommon and included headache and diarrhea; these were usually mild and temporary.

What is Juluca?

Juluca contains two medicines—dolutegravir and rilpivirine. Dolutegravir belongs to the class of drugs called integrase inhibitors. Rilpivirine belongs to the class of drugs called non-nucleoside reverse transcriptase inhibitors ("non-nukes" or NNRTIs).

How does Juluca work?

The drugs in Juluca work by interfering with enzymes needed by HIV called integrase and reverse transcriptase. Using Juluca greatly reduces HIV's ability to infect cells and make copies of itself.

How do people with HIV use Juluca?

Juluca is meant as a replacement for a person's current HIV regimen. The manufacturer of Juluca, ViiV, recommends that a person's viral load prior to starting Juluca should be stable and undetectable. For more information about HIV treatment, see CATIE's *Your Guide to HIV Treatment*.

For many people with HIV, the use of ART (HIV treatment or antiretroviral therapy) has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to greatly reduce the risk of developing a life-threatening infection or an AIDS-related cancer. Neither Juluca nor any other treatment regimen (ART) is a cure for HIV. It is therefore important that you see your doctor for checkups and lab tests on a regular basis.

Evidence shows that HIV-positive people who are on ART, engaged in care, and have an ongoing undetectable viral load are substantially less likely

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to transmit HIV to others, be it through sex, when sharing equipment to use drugs or during pregnancy and birth. In fact, the evidence for sexual transmission shows that people on ART who maintain an undetectable viral load do not pass HIV to their sexual partners. For further information see the CATIE fact sheet *HIV treatment and an undetectable viral load to prevent HIV transmission*. However, it is still a good idea to use condoms because they can reduce your risk for getting and passing on other sexually transmitted infections.

Warnings

Anxiety and depression

Although not common in clinical trials, a small proportion of people (less than 2%) who took Juluca developed depression, negative thoughts, anxiety and thoughts of suicide that led to attempted suicide.

Anxiety and depression are relatively common in HIV-positive people (regardless of whether they are on treatment or the type of treatment that they take). If you are taking Juluca and think that you may have developed anxiety or depression, speak to your doctor right away. Your doctor can help determine if you have anxiety or depression and if there is any relationship between them and the medicines that you are taking.

Symptoms of anxiety and depression can include the following:

- becoming easily upset or angry
- feeling fearful
- excessive worry
- difficulty falling asleep or staying asleep, or waking up prematurely
- unexpected feelings of sadness
- recurrent nightmares
- prolonged feelings of sadness, anger or depression
- feeling hopeless
- loss of pleasure in everyday activities
- unexpectedly feeling tired or experiencing a lack of energy
- strange thoughts

If you have any of these feelings, contact your doctor or nurse right away.

If you have thoughts of harming yourself or others, dial 911 right away.

Pregnancy

In May 2018, regulatory agencies, including Health Canada, the U.S. Food and Drug Administration and the European Medicines Agency, issued cautionary statements because dolutegravir was associated with an apparent increased risk of birth defects in a clinical trial in the southern African country of Botswana. Specifically, HIV-positive women who used dolutegravir at the time of conception appeared to have a small but increased risk of giving birth to infants with a type of birth defect called a neural tube defect. This risk was greater than seen when women used other anti-HIV treatments.

However, long-term data have not found an increased risk of birth defects associated with the use of dolutegravir-containing regimens outside of Botswana, including other African countries, as well as Brazil and the U.S., where there are many people of African descent. There has not been an increased risk of birth defects linked to dolutegravir-containing regimens in Canada. Furthermore, the number of children born with such birth defects in Botswana to women who used dolutegravir was limited. Also, over the course of several years in the same study, the risk of giving birth to an infant with a birth defect decreased among women who used dolutegravir at the time of conception.

The good news is that the latest data from Botswana indicate that the level of birth defects in infants born to women who use dolutegravir at the time of conception is now very low and similar to that seen in women who use other anti-HIV drugs at the time of conception.

If you are taking Juluca and are pregnant or want to have a baby, let your doctor know.

Skin and hypersensitivity reactions

In large clinical trials with Juluca, about 1% of participants developed rash. All rashes were of mild or moderate severity.

However, over the past decade there are reports of people using dolutegravir or rilpivirine (the drugs in Juluca) who developed severe skin and hypersensitivity reactions. Symptoms of hypersensitivity reactions can include severe rash or rash with a fever, together with lack of energy and painful muscles or joints. In clinical trials, some severe cases with additional symptoms occurred, such as peeling of the skin, blisters on the lips, swollen eyes and face, stomach cramps and difficulty breathing. The manufacturer advises that Juluca (or any other drugs suspected of causing this reaction) should be discontinued immediately if these symptoms occur, otherwise the hypersensitivity reaction can become life threatening. If symptoms suggestive of hypersensitivity occur, see your doctor immediately or go to the emergency room of your nearest hospital or medical centre.

Liver health

People who are co-infected with hepatitis B or C viruses or who have elevated levels of liver enzymes in the blood prior to initiating Juluca may be at risk for liver inflammation or injury. According to ViiV, both rilpivirine and dolutegravir use have been linked to "a few cases of [liver injury]." None of the people who developed liver injury had any known pre-existing factors that placed them at heightened risk of liver injury. Therefore, ViiV states that "Appropriate laboratory testing prior to initiating therapy and monitoring for [liver injury] during therapy with Juluca is recommended."

Age

Juluca has not been tested in people younger than 18 years. Juluca has also not been tested in large numbers of people who are 65 years or older so its effectiveness and safety in these populations is not known.

Side effects

1. General

In clinical trials, Juluca was well tolerated, generally safe and effective. However, as with any treatment, there were side effects but these were usually mild and temporary and included the following:

- headache
- nausea
- diarrhea

Note that the HIV-positive people who are typically enrolled in pivotal clinical trials of HIV treatments, including Juluca, are generally young and healthy. Once a drug is approved and more widely available, it gets used by populations who are not usually in pivotal clinical trials. These people may be older and may have other health issues—such as cardiovascular disease, liver injury, kidney injury, type 2 diabetes, anxiety, depression, and substance use—that require medications or that cause symptoms. As a result, their experience of side effects may be different from those reported in pivotal clinical trials.

2. Weight gain

Some studies with HIV-positive people who used dolutegravir as part of combination treatment found that weight gain occurred. In some people the increased weight gain was modest—a few kilos—while in others it was more substantial. Research suggests that some HIV-positive people with the following features or characteristics tend to gain weight when on ART:

- women
- people of African, Black or Caribbean descent
- people whose CD4+ cell count fell below the 200 cell/mm^3 level at some point in the past.

However, some HIV-positive people without these features can also gain weight. The cause of increased weight in HIV-positive people is not clear because studies suggest that HIV-negative people of the same age and gender are also generally gaining weight even though they are not taking ART.

An increase of one or two kilograms in weight over the course of one year is normal when initiating ART and is what has been reported in clinical trials in the current era. However, should you gain more than this amount of weight, speak to your nurse or doctor so that your weight gain can be assessed. Doctors and nurses also take into account a person's waist size and/or body mass index (BMI) – this is a number derived by dividing their height by the square of their weight. If your nurse or doctor has found that your BMI is increasing and is outside what is considered healthy then they will investigate possible causes for an increase in weight.

There may be one or more reasons that your BMI is increasing, including the following:

Physical activity – Are you getting enough daily physical activity, including walking and climbing stairs? If not, can you begin a program of exercise? Speak to your nurse or doctor about what kind of exercise is right for you.

Sleeping problems – Rest and sleep quality are sometimes overlooked aspects of health. A large observational study in HIV-negative people found that people who have sleeping problems tend to gain weight. If you are unexpectedly gaining weight, speak to your doctor or nurse to rule out any sleep problems.

Emotional and mental health – Are there factors in your life that can affect how you respond to stressful events? For instance, when stressed, some people eat more fat and carbohydrate-rich foods as a source of comfort. Repeated engagement in excessive intake of carbohydrates and fatty foods can lead to weight gain over time. Depression can affect appetite—some people gain weight, others lose weight. If you notice weight gain along with changes in your mood, speak to your doctor or nurse.

Metabolic conditions, hormones and arthritis

Some conditions and life-stages are associated with weight gain, including the following:

- pre-diabetes and diabetes
- problems with the thyroid gland and its hormones
- being post-menopausal
- arthritis

Diet

Not everyone follows a diet that is informed by dietary guidelines. If you have access to subsidized dietary counselling (sometimes this is provided in large hospitals and clinics), you may benefit from consulting a registered dietitian. Registered dietitians can assess the quality and quantity of meals, and if necessary, provide helpful advice about making healthy changes.

Substance use

Alcohol contains calories. Is excess consumption of alcohol an issue for you? Excess consumption of alcoholic beverages could suggest unaddressed mental health and emotional issues.

Prescription medicines

Some prescription medicines (for conditions other than HIV) have the potential to cause changes in weight, particularly increased weight. It can be useful to speak to a pharmacist about all the medicines that you are taking to see if any are associated with changes in weight. You can then discuss any medicines that your pharmacist has identified with your doctor.

Bear in mind

While the above list covers some potential causes of weight gain in HIV-positive people, it is not exhaustive.

3. The kidneys

The kidneys filter the blood, put waste materials into urine and reabsorb nutrients and other useful materials back into the blood. Juluca contains dolutegravir and this drug can interfere with the ability of the kidneys to release the waste product creatinine into urine. Therefore, a small but persistent increase of creatinine levels in the blood is generally seen in dolutegravir users. This small increase is not considered harmful by researchers.

Furthermore, this effect on creatinine does not appear to affect the ability of the kidneys to filter other substances. Such an effect on creatinine is also seen with the anti-ulcer drug cimetidine (Tagamet) and with the boosting agent cobicistat (found in Stribild) and with the integrase inhibitor bictegravir (in Biktarvy).

4. Uncommon side effects

The following symptoms were uncommon in clinical trials, affecting less than 2% of Juluca users; it is not clear if these symptoms were caused by Juluca, the underlying disease process or something else:

- lack of energy
- abdominal pain
- nausea
- vomiting
- muscle soreness
- decreased appetite
- feeling sleepy during the daytime

Drug interactions

Some drugs (including prescribed and over-the-counter), herbs and supplements can interfere with the absorption and/or effectiveness of Juluca. Such interference is called a drug interaction. Some drugs can reduce the levels of the medicines in Juluca in your blood. This can make Juluca less effective and lead to treatment failure, reducing your future treatment options. Other drugs can raise the levels of medicines in Juluca in your blood, resulting in enhanced side effects or new side effects. Therefore, it is important to disclose to your doctor and pharmacist all the supplements, drugs, and herbs you are taking.

This factsheet is not comprehensive and only lists some of the potential and actual drug interactions with Juluca. Speak to your pharmacist to find out more about drug interactions with Juluca.

Not to be used

ViiV recommends that the following drugs should *not* be used by people taking Juluca:

- for treatment of abnormal heart rhythms – dofetilide (Tikosyn)
- anti-seizure drugs – carbamazepine, oxcarbazepine, phenobarbital and phenytoin
- antibiotics – rifampin, rifapentene
- a class of acid-reducing agents called proton pump inhibitors (PPIs) – Losec (omeprazole), Nexium (esomeprazole), Pantoloc (pantoprazole), Pariet (rabeprazole), Prevacid (lansoprazole)
- for inflammation-related conditions – more than one dose of systemic glucocorticoids (e.g. prednisone, cortisone)
- for treatment of multiple sclerosis – fampridine (also known as dalfampridine)
- herbs – St. John's wort or its extracts, hypericin and hyperforin

Acid-reducing agents, laxatives, metal supplements and buffered medicines

Juluca should be taken at least 4 hours before or 6 hours after taking these medicines. Examples of acid-reducing agents include:

- Alka-Seltzer
- Gaviscon (tablets and syrup)
- Maalox (liquid and tablets)
- Milk of Magnesia
- Pepto-Bismol and Pepto Bismol Childen's
- Rolaids
- Tums
- Zantac (ranitidine), Tagamet (cimetidine)

For supplements containing calcium and/or iron ViiV recommends, "when taken with food, Juluca and calcium and/or iron supplements or multivitamins containing calcium and/or iron can be taken at the same time."

Metformin

The drug metformin is commonly used to help manage blood sugar levels. Dolutegravir, in Juluca, can raise levels of metformin in the body. Your doctor may need to reduce your dose of metformin if you are also taking Juluca.

Methadone

In general, no dose adjustment of methadone is necessary. However, ViiV states that clinicians should monitor patients who take Juluca and methadone, as the dose of methadone "may need to be adjusted in some patients."

Resistance and cross-resistance

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes, called mutations, can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed or not taken as prescribed, the level of dolutegravir and rilpivirine in the blood may fall too low. If this happens, the HIV in your body can become resistant to the medication. If you find you are having problems taking your medications as directed, speak to your doctor, nurse or pharmacist about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future options might be, at some point your doctor can have a small sample of your blood analyzed to test for resistance.

Dosage

Juluca is supplied as pink tablets. Each tablet contains 50 mg of dolutegravir and 25 mg of rilpivirine. Juluca is taken once daily with a meal. Juluca must be taken with a meal so that it is absorbed. ViiV states that "a protein-rich nutritional drink or meal replacement drink is not considered a meal."

If you forget to take a dose, ViiV recommends that "you take Juluca with a meal as soon as you remember. If your next dose is due within 12 hours, skip the dose you missed and take the next one at the usual time. Don't take a double dose to make up for the missed dose."

If you have difficulty taking Juluca as prescribed, speak to your healthcare provider.

Availability

Juluca is licensed in Canada. Juluca is meant to replace the current HIV treatment in people whose viral loads are less than 50 copies/mL ("undetectable"). Your doctor or pharmacist can tell you more about the availability and coverage of Juluca in your region. CATIE's online module Federal, Provincial and Territorial Drug Access Programs also contains information about Canadian drug coverage.

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