Risk Management Plan Summary

EDURANT® (rilpivirine)

25 mg
film-coated tablet

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Marketing authorization holder: Janssen-Cilag AG, Gubelstr. 34, 6300 Zug

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of EDURANT is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the product information «Arzneimittelinformation / Information sur le medicament» approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of EDURANT in Switzerland is the «Arzneimittelinformation / Information sur le medicament» (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of EDURANT.

Overview of Disease Epidemiology

Human immunodeficiency virus (HIV) attacks the cells of the immune system, the body's natural defense against germs and other substances that cause infection and illness. Both the virus and the infection it causes are called HIV. Over time the immune system of a person who has HIV may become so weakened that it can no longer fight off infection or the development of certain types of cancer. At this stage, the person is said to have Acquired Immunodeficiency Syndrome (AIDS), which in turn may lead to death.

At the end of 2014, approximately 37 million people around the world were living with HIV. In 2014, approximately 2 million people became newly infected and 1.2 million people died due to HIV. Most people with HIV live in sub-Saharan Africa, home to 70% of all new HIV infections in 2013 (UNAIDS 2015). People with AIDS develop infections or cancers that only rarely occur in people with a healthy immune system. They may also have or develop other kinds of diseases or disorders. The most important ones are:

- coronary artery disease (a disease of the blood vessels that supply blood to the heart muscle)
- dementia (loss of brain function, including memory, thinking, language, judgment, behaviour)
- nerve disorders
- bleeding disorders
- inflammation of the pancreas (a digestive and endocrine organ secreting enzymes that help to break down food and producing hormones that affect the level of sugar in the blood)

In addition, hepatitis B and hepatitis C (infections of the liver) are conditions which co-exist with HIV and are linked with the predisposing factors for HIV infection.

Summary of Treatment Benefits

The active substance in EDURANT is rilpivirine (RPV) that slows down or stops the virus from multiplying. It is a type of anti-HIV medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI). Rilpivirine is to be taken with other anti-HIV medicines to treat HIV-1 infection in adults and in adolescents (12 years of age and above). It is used in people who have never been treated for HIV-1 before. Rilpivirine does not cure HIV infection or AIDS, but it may delay or reverse the damage of the immune system and delay the development of infections and diseases associated with AIDS. In the European Union (EU), RPV is only approved for use in patients who have low blood levels of the HIV virus at the start of HIV treatment because then it was most effective.

Effectiveness was mainly measured by the amount of HIV virus in the blood (called viral load) to see if the drug worked to lower it.

Two major clinical studies involved 1,368 HIV-1 infected adults who had never received anti-HIV drugs before. They were divided into 1 of 2 treatment groups not knowing to which they had been assigned:

- Treatment 1: RPV 25 mg once daily + 2 other anti-HIV drugs
- Treatment 2: efavirenz 600 mg once daily + 2 other anti-HIV drugs (this was the 'control group')

Both studies showed that RPV was effective against HIV-1, even after 96 weeks of treatment (almost 2 years) and that it was well tolerated and has a favourable safety profile.

One study involved 36 adolescents (from 12 to less than 18 years) who had never been treated for HIV-1 before. The safety, tolerability, and efficacy in these adolescents were similar to those observed in adults.

Unknowns Relating to Treatment Benefits

The evidence of the safety and efficacy of RPV is based on the extensive data on RPV in HIV-1 infected adults and a limited number of HIV-1 infected adolescents who have never received anti-HIV drugs before. There is no information about the use of RPV in patients with severely decreased liver or renal function, in children below 12 years, or in breast-feeding women.

There is limited information about the use of RPV in HIV-1 infected patients who have been treated with anti-HIV drugs before, in elderly patients with HIV-1, patients who also have liver infection and in pregnant women.

Summary of Safety Concerns

Important Identified Risks

Risk	What is known	Preventability
Development of drug resistance (the ability of the virus to reproduce during treatment with an anti-HIV drug, making the drug ineffective)	In some patients, the virus becomes resistant to the anti-HIV drug. This may occur during treatment with an NNRTI. When the virus becomes resistant to 1 NNRTI, other NNRTIs and anti-HIV drugs may also not be effective, which limits the number of treatment options available to the patient. The development of resistance to NNRTIs and other anti-HIV drugs was seen more often in adult patients treated with RPV than in adult patients treated with efavirenz.	Yes, by carrying out a blood test to find out if the drug is likely to work for the patient ('resistance testing').
Depression	Depression (including major depression, suicide attempt, or thoughts of suicide) has occurred in patients receiving treatment that included RPV. Depression is common (reported in up to 50%) in HIV patients, regardless of treatment.	No, since no specific risk groups other than patients with a history of psychiatric illness have been identified for depression in patients treated with EDURANT.

Important Potential Risks

Risk	What is known (Including reason why it is considered a potential risk)
Prolongation of the QTc interval (a measurement on an electrocardiogram [ECG] which represents the time during which contraction of the heart ventricles occurs)	In healthy adults, a modest increase in the QTc interval was seen with RPV at a dose of 75 mg once daily or higher (this is higher than the commercial dose used to treat patients who have HIV-1). There is a very small chance that this may lead to more serious heart problems, such as abnormal heart rhythms ('arrhythmias'); very rarely this could lead to sudden death. These risks may be higher when RPV is used with certain other drugs that are known to affect heart rhythm. In the limited number of adolescents studied in TMC278-C213, no ECG-related abnormalities were reported.
Liver effects due to medication ('hepatotoxicity')	Side effects that involve the liver have occurred in patients receiving treatment that included RPV. These side effects (including changes that showed up in blood tests) occurred more often in patients with both HIV-1 infection and liver infection than in patients with only HIV-1 infection.

Risk	What is known (Including reason why it is considered a potential risk)
Severe skin reactions	Patients with HIV are 15 times more likely to visit their doctor for common skin conditions than patients not infected with HIV. These skin conditions can sometimes be caused by other viruses. Acute HIV rash (a skin eruption) can occur with severe skin reactions in 30-50% of patients, but these did not affect patients treated with RPV in the 2 major adult clinical studies or in the adolescent study.
Overdose	It is expected that accidental overdose will be unlikely in patients taking RPV, because the dosing schedule is very simple. The tablet strength is clearly stated on the packaging, and the strength is also printed on each tablet.
Drug use in patients for whom EDURANT is not approved ('Off-label' use in adults and adolescents, and in children <12 years)	Use of EDURANT in HIV-infected patients for whom the drug is not approved may occur, including use in: - children <12 years - adolescents and adults who have not received anti-HIV drugs before but who have high levels of the virus in their blood at the start of treatment - adolescents and adults who have received anti-HIV drugs before Use of RPV in these patients would not necessarily lead to side effects.
Bleeding disorders	A number of bleeding disorders, which result when the blood cannot clot properly, have been reported in patients with HIV. Bleeding disorders also occurred in rats that were given RPV. The patients treated with RPV in clinical studies did not show an increase in bleeding disorders compared to patients treated with efavirenz.
Decreased level of blood cortisol (a stress hormone produced by the adrenal glands)	Decreased cortisol in the blood is often not diagnosed because the signs and symptoms can be caused by a number of other conditions, including HIV. In the 2 major adult clinical studies with RPV, as well as in the study in adolescents, one of the most commonly reported side effects related to glands that secrete hormones was a decrease in the level of cortisol in the blood.

Missing Information

Risk	What is known
Limited information on use in children (<12 years)	Because RPV has not been studied in children under 12 years, no information about its safety or effectiveness in these patients is available. For this reason, use of RPV is not recommended in children under 12 years old.
Limited information on use in pregnant and breast-feeding women	HIV may be carried through the breast milk to the infant during nursing. It is not known whether RPV passes into human breast milk. It is recommended that mothers with HIV do not breast-feed their infants. Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum (TMC114HIV3015). 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). Virologic response was preserved throughout the trial period. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults. Rilpivirine should be used during pregnancy only if the potential benefit justifies the potential risk in the opinion of the treating healthcare professional.
Limited information on use in elderly patients (65 years and older)	Clinical studies with RPV did not include enough patients 65 years and older to determine whether elderly patients respond differently than younger patients. Elderly patients are more likely to have other diseases, including problems with their liver and kidneys, and to take other drugs.
Limited information on use in patients with liver problems	No change in the dose of RPV is required in patients with mildly or moderately decreased liver function. However, RPV should be used with caution in patients with moderately decreased liver function. Rilpivirine has not been studied in patients with severely decreased liver function and is therefore not recommended in these patients.
Limited information on use in patients with kidney problems	No change in the dose of RPV is required in patients with mildly or moderately decreased kidney function. Rilpivirine has not been studied in patients with severely decreased kidney function, and should be used with caution in these patients.
Limited information on use in patients taking anti-HIV drugs that have not been studied in clinical studies	Clinical studies of RPV have only studied RPV when taken with tenofovir disoproxil fumarate and emtricitabine, zidovudine and lamivudine or abacavir and lamivudine. Use of RPV with other anti-HIV drugs has not been studied. However, RPV is not expected to act differently when taken with other anti-HIV drugs.

Summary of Additional Risk Minimisation Measures by Safety Concern

Risk Minimisation Measure(s)

All medicines have a Summary of Product Characteristics (SmPC, also called prescribing information) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

The SmPC and PIL for EDURANT can be found in the EDURANT EPAR page on the EMA website.

This medicine has no additional risk minimisation measures.

Planned Postauthorisation Development Plan

List of studies in postauthorisation development plan

Study/Activity (including study number)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of (interim and) final results
Drug Utilisation Study (DUS) Non-interventional study	To assess the use of EDURANT according to the prescribing information for EDURANT and the development of resistance in routine clinical practice	Important Identified Risk/ -Development of drug resistance Important Potential Risk/ -Off-label use in adults Missing information/ -Patients taking anti-HIV drugs that have not been studied in clinical studies	Started	Final 02Q2019

Studies which are a condition of the marketing authorisation

All the studies listed in the table above are conditions of the marketing authorisation.