EMA/409299/2015
EMEA/H/C/000273

EPAR summary for the public

Rapamune

sirolimus

This document is a summary of the European Public Assessment Report (EPAR) for Rapamune. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Rapamune.

What is Rapamune?

Rapamune is a medicine that contains the active substance sirolimus. It is available as an oral solution (1 mg/ml) and tablets (0.5 mg, 1 mg and 2 mg).

What is Rapamune used for?

Rapamune is used to prevent the body from rejecting a newly transplanted kidney. It is used in adults (aged 18 years or over) who are at a low to moderate risk of rejection. It is recommended that Rapamune be used with ciclosporin and corticosteroids (other medicines to prevent organ rejection) for two to three months. After this period, Rapamune can be used as maintenance treatment together with corticosteroids, but only if ciclosporin treatment can be stopped.

The medicine can only be obtained with a prescription.

How is Rapamune used?

Rapamune treatment should be started by and remain under the guidance of a doctor who is a qualified specialist in transplantation.

Rapamune is given as an initial dose of 6 mg as soon as possible after the transplant, followed by 2 mg once a day for two to three months. The levels of sirolimus in the patient's blood should be monitored, and the dose of Rapamune should be adjusted to obtain the appropriate levels of sirolimus (4 to 12 ng/ml). Rapamune should be taken four hours after each ciclosporin dose. Patients should always take Rapamune consistently, either with or without food.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

After this period, Rapamune can be used as 'maintenance therapy' in patients who are able to stop ciclosporin. In these cases, the dose of ciclosporin should be gradually reduced to zero over four to eight weeks, and the dose of Rapamune increased to obtain blood levels of sirolimus of about 12 to 20 ng/ml. On average, the dose of Rapamune needs to be increased fourfold.

How does Rapamune work?

The active substance in Rapamune, sirolimus, is an immunosuppressive agent (a medicine that reduces the activity of the immune system). In the body, sirolimus attaches to a protein that is found inside cells to make a 'complex'. This complex then blocks a protein called 'mammalian target of rapamycin' (mTOR). Since mTOR is involved in the multiplication of activated T-lymphocytes (white blood cells that are responsible for attacking the transplanted organ), Rapamune reduces the number of these cells, reducing the risk of organ rejection.

How has Rapamune been studied?

Rapamune has been studied in two main studies involving a total of 1,295 patients who were having a kidney transplant and were at low to moderate risk of rejection. The first study compared Rapamune oral solution with azathioprine (another immunosuppressive medicine) in 719 patients, and the second compared it with placebo (a dummy treatment) in 576 patients. The medicines were used as an add-on to ciclosporin and corticosteroids. The effectiveness was measured by looking at the number of treatment failures (rejection or loss of the new kidney, or death) after six months.

Two studies looked at Rapamune as maintenance treatment for up to five years in a total of 765 patients who had responded to an initial two- to three-month course of treatment and who were able to stop their dose of ciclosporin.

One additional study compared the ability of the oral solution and the tablets to prevent rejection.

What benefit has Rapamune shown during the studies?

Rapamune was more effective than placebo or azathioprine, when they were added to ciclosporin and corticosteroids. In the first study, 19% of the patients adding Rapamune had failed treatment after six months (53 out of 284), compared with 32% of those adding azathioprine (52 out of 161). In the second study, 30% of the patients adding Rapamune failed treatment (68 out of 277), compared with 48% of those adding placebo (62 out of 130).

The maintenance studies showed that long-term treatment with Rapamune was effective in helping the new kidney to survive, with an improvement in how well the new kidney worked and an improvement in blood pressure when ciclosporin treatment was stopped.

The additional study showed that the oral solution and the tablets were equally effective in preventing rejection.

What is the risk associated with Rapamune?

The most common side effects with Rapamune (seen in more than 1 patient in 10) are pneumonia (infection of the lungs), infections (fungal, viral, bacterial or by *Herpes simplex*), urinary tract infection (infection of the structures that carry urine), thrombocytopenia (low blood platelet counts), anaemia (low red blood cell counts), leucopoenia (low white blood cell counts), hypokalaemia (low blood potassium levels), hypophosphataemia (low blood phosphate levels), hyperlipidaemia (including

hypercholesterolaemia (high blood cholesterol levels) and hypertriglyceridaemia (high blood levels of triglycerides, a type of fat)), hyperglycaemia (high blood sugar levels), diabetes, headache, tachycardia (rapid heartbeat), lymphocele (fluid collection around the kidney), hypertension (high blood pressure), abdominal pain (stomach ache), diarrhoea, constipation, nausea (feeling sick), rash, acne, arthralgia (joint pain), proteinuria (protein in the urine), menstrual disorders, oedema (swelling), peripheral oedema (swelling of the ankles and feet), pyrexia (fever), pain, impaired wound healing, increased blood lactate dehydrogenase levels (a marker of tissue breakdown), increased blood creatinine levels (a marker of kidney problems) and abnormal liver function test. Because it reduces the activity of the immune system, Rapamune can also increase the risk of developing cancer, especially lymphoma and skin cancer. For the full list of all side effects reported with Rapamune, see the package leaflet.

Patients allergic to peanut or soya must not take Rapamune oral solution because the solution contains soya oil. For the full list of restrictions, see the package leaflet.

Why has Rapamune been approved?

The CHMP decided that Rapamune's benefits are greater than its risks and recommended that it be given marketing authorisation.

What measures are being taken to ensure the safe and effective use of Rapamune?

A risk management plan has been developed to ensure that Rapamune is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Rapamune, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Rapamune

The European Commission granted a marketing authorisation valid throughout the European Union for Rapamune on 14 March 2001.

The full EPAR for Rapamune can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports. For more information about treatment with Rapamune, read the Package Leaflet (also part of the EPAR) or contact your doctor or pharmacist.

This summary was last updated in 06-2015.