European Medicines Agency

EMEA/H/C/712

EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

ADVAGRAF

EPAR summary for the public

This document is a summary of the European Public Assessment Report (EPAR). It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the studies performed, to reach their recommendations on how to use the medicine.
If you need more information about your medical condition or your treatment, read the Package Leaflet (also part of the EPAR) or contact your doctor or pharmacist. If you want more information on the basis of the CHMP recommendations, read the Scientific Discussion (also part of the EPAR).

What is Advagraf?

Advagraf is a medicine containing the active substance tacrolimus. It is available as prolonged-released capsules containing tacrolimus (0.5 mg: yellow and orange; 1 mg: white and orange; 5 mg: greyish-red and orange). 'Prolonged-release' means that tacrolimus is released slowly from the capsule over a few hours.

What is Advagraf used for?

Advagraf is used in adult patients who have had a kidney or liver transplant, to prevent rejection (when the immune system attacks the transplanted organ). Advagraf can also be used to treat organ rejection in adult patients when other immunosuppressive medicines are not effective.
The medicine can only be obtained with a prescription.

How is Advagraf used?

Treatment with Advagraf should only be prescribed by doctors who have experience in the management of transplant patients.
Advagraf is for long-term use. Doses are calculated based on the patient's weight. Doctors should monitor the levels of tacrolimus in the blood to check that they stay within predefined ranges.
In the prevention of rejection, the dose of Advagraf to use depends on the type of transplant the patient has received. In kidney transplant, the starting dose is 0.20 to 0.30 mg per kilogram body weight. In liver transplant, the starting dose is 0.10 to 0.20 mg/kg.
When treating rejection, these same doses may be used in kidney and liver transplants. Starting doses are 0.10 to 0.30 mg/kg in other types of transplant (heart, lung, pancreas or intestine).
Advagraf is given once a day, in the morning, at least one hour before or two to three hours after food.

How does Advagraf work?

Tacrolimus, the active substance in Advagraf, is an immunosuppressive agent. This means that it reduces the activity of the immune system (the body's natural defences). Tacrolimus acts on some special cells in the immune system called T-cells that are primarily responsible for attacking the transplanted organ (organ rejection).
Tacrolimus has been used since the mid-1990's. In the European Union (EU), it has been available as capsules under the name Prograf or Prograft (depending on the country). Advagraf is very similar to Prograf/Prograft, but the way the medicine is made has been changed so that the active substance is

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released more slowly from the capsule than it is in Prograf/Prograft. This allows Advagraf to be given once a day, whereas Prograf/Prograft is given twice a day. This can help the patients stick to their treatment.

How has Advagraf been studied?
Because tacrolimus and Prograf/Prograft have already been used in the EU, the company presented the results of studies that had been carried out with Prograf/Prograft previously, as well as data from the published literature. It also presented the results of a clinical study in 668 kidney transplant patients comparing the use of Advagraf with that of Prograf/Prograft or ciclosporin (another immunosuppressive medicine used in the prevention of rejection). Patients also received mycophenolate mofetil (another medicine used in the prevention of rejection). The main measure of effectiveness was the number of patients in whom the transplant failed (as measured by looking at, for example, the need for a repeat transplant or a return to dialysis) after one year's treatment. Further shorter studies were also carried out in 119 kidney transplant patients and 129 liver transplant patients, looking at how Advagraf is absorbed by the body in comparison to Prograf/Prograft.

What benefit has Advagraf shown during the studies?
Advagraf was as effective as both comparator medicines. After one year, 14% of the patients receiving Advagraf had experienced organ failure. The percentages were 15% in the patients treated with Prograf/Prograft, and 17% in those treated with ciclosporin. The shorter studies in kidney and liver transplant patients showed that Advagraf and Prograf/Prograft have comparable absorption in the body.

What is the risk associated with Advagraf?
The most common side effects with Advagraf (seen in more than 1 patient in 10) are tremor (shaking), headache, nausea (feeling sick), diarrhoea, kidney problems, hyperglycaemia (raised blood glucose levels), diabetes, hyperkalaemia (raised blood potassium levels), hypertension (high blood pressure) and insomnia (difficulty sleeping). For the full list of all side effects reported with Advagraf, see the Package Leaflet.
Advagraf should not be used in people who may be hypersensitive (allergic) to tacrolimus, to macrolide antibiotics (such as erythromycin) or to any of the other ingredients.
Patients and doctors must be careful when other medicines (including some herbal remedies) are taken at the same time as Advagraf, as there may be a need to adjust the dose of Advagraf or the dose of the medicine it is taken with. See the Package Leaflet for details.

Why has Advagraf been approved?
The Committee for Medicinal Products for Human Use (CHMP) decided that Advagraf's benefits are greater than its risks for the prophylaxis of transplant rejection in adult kidney and liver allograft recipients, and in the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients. The Committee recommended that Advagraf be given marketing authorisation.

Other information about Advagraf:
The European Commission granted a marketing authorisation valid throughout the EU for Advagraf on 23 April 2007. The marketing authorisation holder is Astellas Pharma Europe B.V.

The full EPAR for Advagraf can be found here.

This summary was last updated in 02-2008.