Package leaflet: Information for the patient

Advagraf 0.5 mg prolonged-release hard capsules
Advagraf 1 mg prolonged-release hard capsules
Advagraf 3 mg prolonged-release hard capsules
Advagraf 5 mg prolonged-release hard capsules
Tacrolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs and illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Advagraf is and what it is used for
Advagraf contains the active substance tacrolimus. It is an immunosuppressant. Following your organ transplant (liver, kidney), your body's immune system will try to reject the new organ. Advagraf is used to control your body's immune response, enabling your body to accept the transplanted organ.

You may also be given Advagraf for an ongoing rejection of your transplanted liver, kidney, heart or other organ when any previous treatment you were taking was unable to control this immune response after your transplantation.

Advagraf is used in adults.

2. What you need to know before you take Advagraf

Do not take Advagraf
- if you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Advagraf (see section 6).
- if you are allergic to sirolimus or to any macrolide-antibiotic (e.g. erythromycin, clarithromycin, josamycin).

Warnings and precautions
Prograf and Advagraf both contain the active substance, tacrolimus. However, Advagraf is taken once daily, whereas Prograf is taken twice daily. This is because Advagraf capsules allow for a prolonged release (more slow release over a longer period) of tacrolimus. Advagraf and Prograf are not interchangeable.

Tell your doctor if any of the following apply to you:
- if you are taking any medicines mentioned below under 'Other medicines and Advagraf'.
- if you have or have had liver problems
- if you have diarrhoea for more than one day

- if you feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting
- if you have an alteration of the electrical activity of your heart called “QT prolongation”.

Tell your doctor immediately if during treatment you suffer from:

problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.

Your doctor may need to adjust your dose of Advagraf.

You should keep in regular contact with your doctor. From time to time, your doctor may need to do blood, urine, heart, eye tests, to set the right dose of Advagraf.

You should limit your exposure to the sun and UV (ultraviolet) light whilst taking Advagraf. This is because immunosuppressants could increase the risk of skin cancer. Wear appropriate protective clothing and use a sunscreen with a high sun protection factor.

Children and adolescents
The use of Advagraf is not recommended in children and adolescents under 18 years.

Other medicines and Advagraf
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal preparations.

It is not recommended that Advagraf is taken with ciclosporin (another medicine used for the prevention of transplant organ rejection).

Advagraf blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Advagraf, which may require interruption, an increase or a decrease in Advagraf dose. In particular, you should tell your doctor if you are taking or have recently taken medicines like:
- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g. ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, and isavuconazole, erythromycin, clarithromycin, josamycin, and rifampicin
- letermovir, used to prevent illness caused by CMV (human cytomegalovirus)
- HIV protease inhibitors (e.g ritonavir, nelfinavir, saquinavir), the booster medicine cobicistat, and combination tablets, used to treat HIV infection
- HCV protease inhibitors (e.g. telaprevir, boceprevir, and the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir), used to treat hepatitis C infection
- nilotinib and imatinib (used to treat certain cancers)
- mycophenolic acid, used to suppress the immune system to prevent transplant rejection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- cisapride or the antacid magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill or other hormone treatments with ethinylestradiol, hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g. nifedipine, nicardipine, diltiazem and verapamil)
- anti-arrhythmic drugs (amiodarone) used to control arrhythmia (uneven beating of the heart)
- medicines known as “statins” used to treat elevated cholesterol and triglycerides
- phenytoin or phenobarbital, used to treat epilepsy
- the corticosteroids prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression

- Herbal preparations containing St. John's Wort (*Hypericum perforatum*) or extracts of *Schisandra sphenanthera*.

Tell your doctor if you are taking or need to take ibuprofen (used to treat fever, inflammation and pain), amphotericin B (used to treat bacterial infections) or antivirals (used to treat viral infections e.g. aciclovir). These may worsen kidney or nervous system problems when taken together with Advagraf.

Your doctor also needs to know if you are taking potassium supplements or certain diuretics used for heart failure, hypertension and kidney disease, (e.g. amiloride, triamterene, or spironolactone), non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes, while you take Advagraf.

If you need to have any vaccinations, please tell your doctor before.

Advagraf with food and drink
Avoid grapefruit (also as juice) while on treatment with Advagraf, since it can affect its levels in the blood.

Pregnancy and breast-feeding
If you are, think you might be or are planning to become pregnant, ask your doctor for advice before using Advagraf.
Advagraf passes into breast milk. Therefore, you should not breast-feed whilst using Advagraf.

Driving and using machines
Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking Advagraf. These effects are more frequent if you also drink alcohol.

Advagraf contains lactose, sodium and lecithin (soya)
Advagraf contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.
The printing ink used on Advagraf capsules contains soya lecithin. If you are allergic to peanut or soya, talk to your doctor to determine whether you should use this medicine.

3. How to take Advagraf

Always take Advagraf exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. This medicine should only be prescribed to you by a doctor with experience in the treatment of transplant patients.

Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine. This medicine should be taken once a day. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial daily doses just after transplantation will generally be in the range of

0.10 – 0.30 mg per kg body weight per day

depending on the transplanted organ. When treating rejection, these same doses may be used.

Your dose depends on your general condition and on which other immunosuppressive medication you are taking.

Following the initiation of your treatment with Advagraf, frequent blood tests will be taken by your doctor to define the correct dose. Afterwards regular blood tests by your doctor will be required to define the correct dose and to adjust the dose from time to time. Your doctor will usually reduce your Advagraf dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take.

You will need to take Advagraf every day as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.

Advagraf is taken orally once daily in the morning. Take Advagraf on an empty stomach or 2 to 3 hours after a meal. Wait at least 1 hour until the next meal. Take the capsules immediately following removal from the blister. The capsules should be swallowed **whole** with a glass of water. Do not swallow the desiccant contained in the foil wrapper.

If you take more Advagraf than you should
If you have accidentally taken too much Advagraf, contact your doctor or nearest hospital emergency department immediately.

If you forget to take Advagraf
If you have forgotten to take your Advagraf capsules in the morning, take them as soon as possible on the same day. Do not take a double dose the next morning.

If you stop taking Advagraf
Stopping your treatment with Advagraf may increase the risk of rejection of your transplanted organ. Do not stop your treatment unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Advagraf can cause side effects, although not everybody gets them.

Advagraf reduces your body's defence mechanism (immune system), which will not be as good at fighting infections. Therefore, you may be more prone to infections while you are taking Advagraf.

Severe effects may occur, including allergic and anaphylactic reactions. Benign and malignant tumours have been reported following Advagraf treatment.

Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), agranulocytosis (a severely lowered number of white blood cells), haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown) and febrile neutropenia (a decrease in the type of white blood cells which fight infection, accompanied by fever) have been reported. It is not known exactly how often these side effects occur.

<u>Very common side effects (may affect more than 1 in 10 people):</u>
- Increased blood sugar, diabetes mellitus, increased potassium in the blood
- Difficulty in sleeping
- Trembling, headache
- Increased blood pressure
- Liver function tests abnormal
- Diarrhoea, nausea
- Kidney problems

Common side effects (may affect up to 1 in 10 people):

- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts (seen in blood tests)
- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts (seen in blood tests)
- Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- Fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- Blurred vision, increased sensitivity to light, eye disorders
- Ringing sound in your ears
- Reduced blood flow in the heart vessels, faster heartbeat
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- Shortness in breath, disorders of the respiratory tissues in the lung, collection of liquid around the lung, inflammation of the pharynx, cough, flu-like symptoms
- Stomach problems such as inflammation or ulcer causing abdominal pain or diarrhoea, bleeding in the stomach, inflammation or ulcer in the mouth, collection of fluid in the belly, vomiting, abdominal pain, indigestion, constipation, passing wind, bloating, loose stools
- Bile duct disorders, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- Itching, rash, hair loss, acne, increased sweating
- Pain in joints, limbs, back and feet, muscle spasms
- Insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- General weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling of temperature disturbed
- Insufficient function of your transplanted organ

Uncommon side effects (may affect up to 1 in 100 people):

- Changes in blood clotting, reduction in the number of all types of blood cells (seen in blood tests)
- Dehydration, inability to urinate
- Abnormal blood test results: reduced protein or sugar, increased phosphate, increase of the enzyme lactate dehydrogenase
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- Clouding of the eye lens, impaired hearing
- Irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
- Blood clot in a vein of a limb, shock
- Difficulties in breathing, respiratory tract disorders, asthma
- Obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
- Inflammation of the skin, burning sensation in the sunlight
- Joint disorders
- Painful menstruation and abnormal menstrual bleeding
- Multiple organ failure, flu-like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, weight loss

Rare side effects (may affect up to 1 in 1,000 people):

- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Blindness, deafness
- Collection of fluid around the heart
- Acute breathlessness

- Cyst formation in your pancreas
- Problems with blood flow in the liver
- Serious illness with blistering of skin, mouth, eyes and genitals; increased hairiness
- Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer

Very rare side effects (may affect up to 1 in 10,000 people):
- Muscular weakness
- Abnormal heart scan
- Liver failure
- Painful urination with blood in the urine
- Increase of fat tissue

Not known (frequency cannot be estimated from the available data):
- Abnormality of the optic nerve (optic neuropathy)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Advagraf

Keep out of the sight and reach of children.

Do not use Advagraf after the expiry date which is stated on the carton after "Exp". The expiry date refers to the last day of that month. Use all the prolonged-release hard capsules within 1 year of opening the aluminium wrapping.

Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Advagraf contains
- The active substance is tacrolimus.
  Each capsule of Advagraf 0.5 mg contains 0.5 mg of tacrolimus (as monohydrate).
  Each capsule of Advagraf 1 mg contains 1 mg of tacrolimus (as monohydrate).
  Each capsule of Advagraf 3 mg contains 3 mg of tacrolimus (as monohydrate).
  Each capsule of Advagraf 5 mg contains 5 mg of tacrolimus (as monohydrate).

- The other ingredients are:
  Capsule content: Hypromellose, ethylcellulose, lactose, magnesium stearate.
  Capsule shell: Titanium dioxide (E171), yellow iron oxide (E 172), red iron oxide (E 172), sodium laurilsulfate, gelatin.
  Printing ink: Shellac, lecithin (soya), simeticone, red iron oxide (E 172), hydroxypropylcellulose.

What Advagraf looks like and contents of the pack
Advagraf 0.5 mg prolonged-release hard capsules are hard gelatin capsules imprinted in red with "0.5 mg" on the light yellow capsule cap and "★ 647" on the orange capsule body, containing white powder.
Advagraf 0.5 mg is supplied in blisters or perforated unit-dose blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50 and 100 prolonged-release capsules are

available in blisters and packs of 30×1, 50×1 and 100×1 prolonged-release capsules are available in perforated unit-dose blisters.

Advagraf 1 mg prolonged-release hard capsules are hard gelatin capsules imprinted in red with “1 mg” on the white capsule cap and “★ 677” on the orange capsule body, containing white powder.
Advagraf 1 mg is supplied in blisters or perforated unit-dose blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50, 60 and 100 prolonged-release capsules are available in blisters and packs of 30×1, 50×1, 60×1 and 100×1 prolonged-release capsules are available in perforated unit-dose blisters.

Advagraf 3 mg prolonged-release hard capsules are hard gelatin capsules imprinted in red with “3 mg” on the orange capsule cap and “★ 637” on the orange capsule body, containing white powder.
Advagraf 3 mg is supplied in blisters or perforated unit-dose blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50 and 100 prolonged-release capsules are available in blisters and packs of 30×1, 50×1 and 100×1 prolonged-release capsules are available in perforated unit-dose blisters.

Advagraf 5 mg prolonged-release hard capsules are hard gelatin capsules imprinted in red with “5 mg” on the greyish red capsule cap and “★ 687” on the orange capsule body, containing white powder.
Advagraf 5 mg is supplied in blisters or perforated unit-dose blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50 and 100 prolonged-release hard capsules are available in blisters and packs of 30×1, 50×1 and 100×1 prolonged-release capsules are available in perforated unit-dose blisters.

Not all pack sizes may be marketed.

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Manufacturer:
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Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/.