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 the **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 this medicine after the expiry date which is stated on the label 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.
- If the capsules become discoloured or show any other signs of deterioration, you should seek the advice of your pharmacist who will tell you what to do.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Advagraf™ contains

- The active substance is tacrolimus.
- 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™ 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™ is supplied in blisters containing 10 capsules within a protective foil wrapper, including a desiccant.
Advagraf™ is available in blisters packs of 50×1 prolonged-release capsules.

Manufacturer:

Astellas Ireland Co., Ltd., Killorglin, County Kerry, V93 FC86, Ireland.

Procured from within the EU and repackaged by the Product Licence Holder Beachcourse Ltd., Unit 2-3, Townsend Industrial Estate, Waxlow Road, London, NW10 7NU.

PL 16378/1146 **POM**

Revision date: 28.03.2025

Advagraf™ is a trademark of Astellas Pharma Inc.

Blind or partially sighted?
Is this leaflet hard to see or read?
Phone Beachcourse,
Tel: 020 8896 9054 for help.
Ref. number: 1146/V2

Package leaflet: Information for the patient

Advagraf™ 5 mg prolonged-release hard capsules

(tacrolimus)

Your medicine is known by the above name, but will be referred to as Advagraf™ throughout this leaflet.

This medicine is also available in other strengths.

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 of 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.

Talk to your doctor or pharmacist before taking Advagraf™:

- 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”.
- if you have or have had damage to the smallest blood vessels, known as thrombotic microangiopathy/ thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome. Tell your doctor if you develop fever, bruising under the skin (which may appear as red dots), unexplained tiredness, confusion, yellowing of the skin or eyes, reduced urine output, vision loss and seizures (see section 4). When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase.

Please avoid taking any herbal remedies, e.g., St. John’s wort (*Hypericum perforatum*) or any other herbal products as this may affect the effectiveness and the dose of Advagraf™ that you need to receive. If in doubt please consult your doctor prior to taking any herbal products or remedies.

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.

Precaution for handling:

Direct contact with any part of your body like your skin or eyes, or breathing in of injection solutions, powder or granules contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and eyes.

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).

If you need to attend a doctor other than your transplant specialist, tell the doctor that you are taking tacrolimus. Your doctor may need to consult your transplant specialist if you should use another medicine that could increase or decrease your tacrolimus blood level.

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.

Some patients have experienced increases in tacrolimus blood levels while taking other medicines.

This could lead to serious side effects, such as kidney problems, nervous system problems, and heart rhythm disturbances (see section 4).

An effect on the Advagraf™ blood levels may occur very soon after starting the use of another medicine, therefore frequent continued monitoring of your Advagraf™ blood level may be needed within the first few days of starting another medicine and frequently while treatment with the other medicine continues.

Some other medicines may cause tacrolimus blood levels to decrease, which could increase the risk of rejecting the transplanted organ. 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, posaconazole, voriconazole, clotrimazole, isavuconazole, miconazole, caspofungin, telithromycin, erythromycin, clarithromycin, josamycin, azithromycin, rifampicin, rifabutin, isoniazid and flucloxacillin
- 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, or HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine) used to treat HIV infection
- HCV protease inhibitors (e.g., telaprevir, boceprevir, the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir), used to treat hepatitis C infection
- nilotinib and imatinib, idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide, or mitotane (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
- carbamazepine, phenytoin or phenobarbital, used to treat epilepsy
- metamizole, used to treat pain and fever
- 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*
- cannabidiol (uses amongst others include treatment of seizures).

Tell your doctor if you are receiving treatment for hepatitis C. The drug treatment for hepatitis C may change your liver function and may affect blood levels of tacrolimus. Tacrolimus blood levels may fall or may increase depending on the medicines prescribed for hepatitis C. Your doctor may need to closely monitor tacrolimus blood levels and make necessary adjustments of Advagraf™ dose after you start treatment for hepatitis C.

Tell your doctor if you are taking or need to take ibuprofen (used to treat fever, inflammation and pain), antibiotics (cotrimoxazole, vancomycin, or aminoglycoside antibiotics such as gentamicin), amphotericin B (used to treat fungal infections) or antivirals (used to treat viral infections e.g., acyclovir, ganciclovir, cidofovir, foscarnet). These may worsen kidney or nervous system problems when taken together with Advagraf™.

Tell your doctor if you are taking sirolimus or everolimus. When tacrolimus is taken together with sirolimus or everolimus, the risk of developing thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and haemolytic uraemic syndrome may increase (see section 4).

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), or the antibiotics trimethoprim or cotrimoxazole that may increase levels of potassium in your blood, 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™. One study assessed pregnancy outcomes in women treated with tacrolimus and those treated with other immunosuppressants. While there was insufficient evidence in this study to draw conclusions, higher rates of miscarriage were reported among liver and kidney transplant patients treated with tacrolimus, as well as higher rates among kidney transplant patients of persistent hypertension associated with protein loss in the urine that develops during pregnancy or the postpartum period (a condition called pre-eclampsia). No increased risk of major birth defects associated with Advagraf™ use was found.

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 defense 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™.

Some infections could be serious or fatal and may include infections caused by bacteria, viruses, fungi, parasites, or other infections.

Tell your doctor immediately if you get signs of an infection including:

- Fever, cough, sore throat, feeling weak or generally unwell.
- Memory loss, trouble thinking, difficulty walking or loss of vision - these may be due to a very rare, serious brain infection, which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

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

Tell your doctor immediately if you have or suspect you may have any of the following serious side effects:

<u>Serious common side effects (may affect up to 1 in 10 people):</u>

- Gastrointestinal perforation: strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- Insufficient function of your transplanted organ.
- Blurred vision.

<u>Serious uncommon side effects (may affect up to 1 in 100 people):</u>

- Thrombotic microangiopathy (damage to the smallest blood vessels) including haemolytic uraemic syndrome, a condition with the following symptoms: low or no urine output (acute renal failure), extreme tiredness, yellowing of the skin or eyes (jaundice) and abnormal bruising or bleeding and signs of infection.

<u>Serious rare side effects (may affect up to 1 in 1,000 people):</u>

- Thrombotic Thrombocytopenic Purpura: a condition involving damage to the smallest blood vessels and characterised by fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice), with symptoms of acute renal failure (low or no urine output), vision loss and seizures.
- Toxic epidermal necrolysis: erosion and blistering of skin or mucous membranes, red swollen skin that can detach in large parts of the body.
- Blindness.

<u>Serious very rare side effects (may affect up to 1 in 10,000 people):</u>

- Stevens-Johnson syndrome: unexplained widespread skin pain, facial swelling, serious illness with blistering of skin, mouth, eyes and genitals, hives, tongue swelling, red or purple skin rash that spreads, skin shedding.
- *Torsades de pointes:* change in the heart frequency that can be accompanied or not of symptoms, such as chest pain (angina), faint, vertigo or nausea, palpitations (feeling the heartbeat) and difficulty breathing.

<u>Serious side effects – frequency not known (frequency cannot be estimated from the available data):</u>

- Opportunistic infections (bacterial, fungal, viral and protozoal): prolonged diarrhea, fever and sore throat.
- Benign and malignant tumours have been reported following treatment as a result of immunosuppression, including malignant skin cancers and a rare type of cancer that may include skin lesions known as Kaposi’s sarcoma. Symptoms include skin changes such as new or changing discoloration, lesions or lumps.
- Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown accompanied with tiredness) 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. You may have no symptoms or depending on the severity of the condition, you may feel: fatigue, apathy, abnormal paleness of the skin (pallor), shortness of breath, dizziness, headache, chest pain and coldness in hands and feet.
- Cases of agranulocytosis (a severely lowered number of white blood cells accompanied with ulcers in the mouth, fever and infection(s)). You may have no symptoms or you may feel sudden fever, rigors and sore throat.
- Allergic and anaphylactic reactions with the following symptoms: a sudden itchy rash (hives), swelling of hands, feet, ankle, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel you are going to faint.
- Posterior Reversible Encephalopathy Syndrome (PRES): headache, confusion, mood changes, fits, and disturbances of your vision. These could be signs of a disorder known as posterior reversible encephalopathy syndrome, which has been reported in some patients treated with tacrolimus.
- Optic neuropathy (abnormality of the optic nerve): problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or restriction of your field of vision.

The side effects listed below may also occur after receiving Advagraf™ and could be serious:

<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

<u>Common side effects (may affect up to 1 in 10 people):</u>

- 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
- 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, changes in the lung tissue, collection of liquid around the lung, inflammation of the pharynx, cough, flu-like symptoms
- Inflammations or ulcers causing abdominal pain or diarrhoea, bleeding in the stomach, inflammations or ulcers in the mouth, collection of fluid in the belly, vomiting, abdominal pains, indigestion, constipation, flatulence, bloating, loose stools, stomach problems
- 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

<u>Uncommon side effects (may affect up to 1 in 100 people):</u>

- Changes in blood clotting, reduction in the number of all types of blood cells (seen in blood tests)
- Dehydration
- Reduced protein or sugar in the blood, increased phosphate in the blood
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- Opacity 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
- Inability to urinate, 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, increase of the enzyme lactate dehydrogenase in your blood, weight loss

<u>Rare side effects (may affect up to 1 in 1,000 people):</u>

- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Deafness
- Collection of fluid around the heart
- Acute breathlessness
- Cyst formation in your pancreas
- Problems with blood flow in the liver
- Increased hairiness
- Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer

<u>Very rare side effects (may affect up to 1 in 10,000 people):</u>

- Muscular weakness
- Abnormal heart scan
- Liver failure
- Painful urination with blood in the urine
- Increase of fat tissue