Patient package insert in accordance with the pharmacists regulations (preparations)-1986

The medicine is dispensed with a doctor`s prescription only

Advagraf 5 mg	Advagraf 3 mg	Advagraf 1 mg	Advagraf 0.5 mg
Prolonged release capsules	**Prolonged release capsules**	**Prolonged release capsules**	**Prolonged release capsules**

Composition:

Tacrolimus (as monohydrate) 5 mg	Tacrolimus (as monohydrate) 3 mg	Tacrolimus (as monohydrate) 1 mg	Tacrolimus (as monohydrate) 0.5 mg

Read this leaflet carefully in its entirety before using the medicine.

This leaflet contains concise information about the medicine. If you have additional questions, refer to the doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their medical condition appears to be similar.

This medicine is not intended for children or adolescents under the age of 18.

1. What is the medicine used for?

Prevention of graft rejection after a kidney or liver transplant.

Treatment of graft rejection after a kidney or liver transplant, when there is resistance to other immunosuppressive drugs.

Therapeutic group: immunosuppressant.

2. Before using the medicine:

Do not use the medicine:

- If you are sensitive (allergic) to tacrolimus or to any of the additional ingredients that the medicine contains.

- If you are sensitive (allergic) to sirolimus or to antibiotics of the macrolide family (such as erythromycin, clarithromycin, josamycin).

Special warnings for using the medicine:

Prograf and Advagraf contain both 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.

You must update the doctor in the following cases:

- If you are taking a medicine in the list appearing in the next section ("if you are taking or have recently taken medicines…").
- If you have or have had liver problems.
- If you have diarrhea 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".

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 have to change your Advagraf dose.

You must be in regular contact with your doctor. From time to time your doctor will have to conduct urine, blood, heart or eye tests to determine the correct dose of Advagraf.

You must avoid exposure to the sun or to UV (ultraviolet) light while 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.

If you are taking or have recently taken other medicines, including non-prescription medicines and food supplements, tell the doctor or pharmacist

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.

You must inform the doctor or pharmacist if you are taking:

- Drugs and antibiotics for treating fungal infections such as ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, clotrimazole, isavuconazole, and miconazole.
- Antibiotics, particularly of the macrolide family for treating infections, such as 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.
- Drugs for treating peptic ulcer and gastroesophageal reflux disorder (such as 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*.

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.

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.

Use of the medicine and food: you must avoid eating grapefruit and drinking grapefruit juice during treatment with Advagraf because this may affect the blood drug levels.

Use of the medicine and consuming alcohol: consuming alcohol while taking the medicine may increase side effects of drowsiness, dizziness and blurred vision.

Pregnancy and breastfeeding:
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.

Important information on some of the medicine ingredients: the medicine contains lactose, sodium and soya (lecithin).

Advagraf contains lactose. You must update the doctor if you are aware that you suffer from intolerance to certain types of sugar.
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.
The ink that is used for printing on the capsule contains soya, if you are sensitive to soya or to peanuts, you must update the doctor in order to decide whether it is worth using the medicine.

3. How will use the medicine?

Always use according to the doctor's instructions.

You must check with the doctor or pharmacist if you are unsure.

The dose and treatment regimen will be determined by the doctor only.

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 initial dose for prevention of rejection of the transplanted organ will be calculated by the doctor in accordance with your body weight. The initial dose after transplantation is usually 0.1-0.3 mg per kg of body weight per day, depending on the transplanted organ. The dose for treating of graft rejection is identical.

The dose that you are receiving depends on your general condition and the additional immunosuppressive drug types that you are taking.

You must take Advagraf every day, for as long as you need immunosuppressive therapy for preventing graft rejection. You must be in constant contact with your doctor.

Tests and follow up

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.

How to use:

- You must take the medicine once a day, in the morning hours on an empty stomach or 2-3 hours after a meal.
- You must wait at least 1 hour until the next meal.
- Take the capsules immediately following removal from the blister.
- Do not chew or crush the capsules.
- The capsules should be swallowed whole with a glass of water.
- Do not swallow the desiccant that is enclosed in the foil wrapper.

If you have accidentally taken an overdose or if a child has accidentally swallowed some of the medicine refer immediately to a doctor or to a hospital emergency department and bring the package of the medicine with you.

If you have forgotten to take this medicine in the morning take a dose as soon as you remember on the same day. You must not take two doses together on the following morning under any circumstances!
You must adhere to the treatment as recommended by the doctor.

Even if an improvement has occurred in your health, you must not stop taking the medication without consulting the doctor. Do not stop taking the medicine without an instruction from the doctor.

If you stop taking the medicine: stopping taking the medicine may increase the risk for graft rejection. Do not stop taking the medicine without an instruction from the doctor:

Do not take drugs in the dark! Check the label and the dose every time you take a drug. Wear glasses if you need them.

If you have additional questions concerning the use of the medicine, consult the physician or pharmacist.

4. Side effects:

As with any medicine, use of Advagraf may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.

Advagraf suppresses the activity of the immune system, meaning that 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 side effects may occur, including allergic and anaphylactic reactions. Benign and malignant tumors have been reported after taking Advagraf.

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

Serious common side effects (may affect up to 1 in 10 people):
- 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.

Serious uncommon side effects (may affect up to 1 in 100 people):
- 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.

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

- Thrombotic Thrombocytopenic Purpura (or TTP) a condition 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).
- Toxic epidermal necrolysis: erosion and blistering of skin or mucous membranes, red swollen skin that can detach in large parts of the body.
- Blindness.

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

- 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.

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

- 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.
- 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:

Very common side effects (may affect more than 1 in 10 people):

- 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
- 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 cramps
- 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, increase of the enzyme lactate dehydrogenase in your blood, 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
- 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

If a side effect has appeared, if one of the side effects worsens, or when you suffer from a side effect that is not mentioned in the leaflet, you must consult the doctor.

Reporting side effects:

Side effects can be reported to the Ministry of Health through a link "report of side effects due to medicine treatment" located in the home page of the Ministry of Health website (www.health.gov.il) refers to online form for reporting side effects or be entering the following link: https://sideeffects.health.gov.il/

5. How to store the medicine

Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach of children and/or infants. By doing so, you will prevent poisoning.

Do not induce vomiting unless explicitly instructed by the doctor.

Do not use the medicine after the expiry date appearing on the package / label. The expiry date refers to the last day of that month.

Shelf life after opening of aluminum wrapping: one year.

Store under 25°C in the original package in order to protect from moisture.

6. Additional information:

In addition to the active substance(s), the medicine also contains:

The capsule content:

Hypromellose, Ethylcellulose, Lactose monohydrate, Magnesium stearate

The capsule shell:

Titanium dioxide(E171), Yellow iron oxide(E172), Red iron oxide(E172), Sodium laurilsulfate, Gelatin

Printing ink:

Shellac, Lecithin (soya), Simeticone, Red iron oxide(E172), Hydroxypropylcellulose

The medicine's appearance and content of the package:

Advagraf 0.5 mg: prolonged-release capsules with the text "0.5 mg" on the light yellow capsule cap and "✶647" on the orange capsule body.

Advagraf 1 mg: prolonged-release capsules with the text "1 mg" on the white capsule cap and "✶677" on the orange capsule body.

Advagraf 3 mg: prolonged-release capsules with the text "3 mg" on the orange capsule cap and "✶637" on the orange capsule body.

Advagraf 5 mg: prolonged-release capsules with the text "5 mg" on the greyish red capsule cap and "✶687" on the orange capsule body.

The product is supplied in packs containing 30, 50 or 100 capsules, not all cases are necessarily marketed.

The registration holder: Astellas Pharma International B.V.

HaMelacha Street Rosh Ha'ayin 4809157 Israel

The manufacturer: Astellas Ireland Co., Ltd. Ireland,
Killorglin, co. Kerry, Ireland

The drug registration numbers in the state drugs registry of the Ministry of Health:

Advagraf 0.5 mg- 34071
Advagraf 1 mg- 34073
Advagraf 3 mg- 34074
Advagraf 5 mg- 34075

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For the sake of simplicity and facilitating reading, this leaflet has been worded in masculine gender. Despite this, the medicine is intended for both sexes.