SCHEDULING STATUS:
South Africa: S4
Namibia: NS2
Kenya: POM

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
ADVAGRAF 0,5 mg prolonged-release capsules
ADVAGRAF 1 mg prolonged-release capsules
ADVAGRAF 5 mg prolonged-release capsules

Read all of this leaflet carefully before you start taking ADVAGRAF.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- ADVAGRAF has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT ADVAGRAF CONTAINS:
ADVAGRAF 0,5 mg (Prolonged-Release Capsules); ADVAGRAF 1 mg (Prolonged-Release Capsules); ADVAGRAF 5 mg (Prolonged-Release Capsules):
Active Ingredient: Each capsule contains 0,5 mg, 1 mg and 5 mg tacrolimus, respectively.
Other ingredients:
Capsule contents: hypromellose, ethylcellulose, lactose monohydrate, magnesium stearate.
Capsule shell: titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E 172), sodium laurilsulfate, gelatin.
Printing ink of capsule shell: shellac, lecithin (soya), simeticone, red iron oxide (E 172), hydroxypropylcellulose.
Contains sugar: lactose

WHAT ADVAGRAF IS USED FOR :
ADVAGRAF is an immunosuppressant and is a prolonged release formulation. 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 or kidney when any previous treatment you were taking was unable to control this immune response after your transplantation.

BEFORE YOU TAKE ADVAGRAF:
Do not take ADVAGRAF:
- If you are allergic (hypersensitive) to tacrolimus or to any antibiotic belonging to the subgroup of macrolide antibiotics (e.g. erythromycin, clarithromycin, josamycin).
- If you are allergic (hypersensitive) to any of the other ingredients of ADVAGRAF.
- If you are pregnant and breastfeeding.
- As ADVAGRAF may alter the metabolism of oral contraceptives, other forms of contraception should also be used.
- With live attenuated vaccines.
- With ciclosporin.
- With grapefruit juice.

Take special care:
- Do not switch between different types of tacrolimus formulations.
- If you are taking any medicines mentioned below under "Taking other medicines with 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 tuberculosis.

- Patients treated with ADVAGRAF have been reported to have an abnormality of some cells in the blood that is associated with a virus that is commonly known as Epstein-Barr Virus (EBV).
- ADVAGRAF should not be administered together with ciclosporin.
- Patients switched to ADVAGRAF rescue therapy should not receive concomitantly anti-lymphocyte treatment.
- Patients treated with ADVAGRAF have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking ADVAGRAF present with symptoms indicating PRES such as headache, altered mental status, seizures and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure control and immediate discontinuation of ADVAGRAF is advised. Most patients completely recover after appropriate measures are taken.
- In view of potential risk of cancers or non-cancerous growths, patients who spend extended periods in the sun, or are otherwise exposed to ultraviolet light, should apply a high protection sun-cream.
- The use of ADVAGRAF is not recommended in children and adolescents under 18 years.

Taking ADVAGRAF with food and drink:
Take ADVAGRAF on an empty stomach one hour before a meal or 2 to 3 hours after a meal. Do not use grapefruit (also as juice) while on treatment with ADVAGRAF, since it can affect its levels in your blood.

Pregnancy and Breastfeeding:
You should not use ADVAGRAF when you are pregnant or breastfeeding your baby.
If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking this medicine.

Driving and using machinery:
ADVAGRAF may cause visual and nervous system disturbances. If you are being treated with ADVAGRAF and you are affected by you should not drive a car or operate dangerous machines. This effect may be made worse when you use ADVAGRAF with alcohol.

Important information about some of the ingredients of ADVAGRAF:
ADVAGRAF contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking ADVAGRAF.
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 ADVAGRAF.

Taking other medicines with ADVAGRAF:
Always tell your healthcare professional if you are taking any other medicine.
(This includes complementary or traditional medicines.)
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, erythromycin, clarithromycin, josamycin, rifampicin and anti-epileptic medicine.
- HIV protease inhibitors (e.g ritonavir, nelfinavir, saquinavir), used to treat HIV infection
- HCV protease inhibitors (e.g. telaprevir, boceprevir), used to treat hepatitis C infection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- 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)
- antidysrhythmic drugs (amiodarone) used to control dysrhythmia (uneven beating of the heart)
- medicines known as “statins” used to treat elevated cholesterol and triglycerides
- phenytoin or phenobarbitone, used to treat epilepsy

- the corticosteroids prednisolone and methylprednisolone (cortisone), 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.

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.

HOW TO TAKE ADVAGRAF:
Do not share medicines prescribed for you with any other person.
Always take ADVAGRAF exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

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.

ADVAGRAF should be taken once a day.

Your doctor will tell you how long your treatment with ADVAGRAF will last. Do not stop treatment early because you may have a rejection of your transplanted organ.
If you have the impression that the effect of ADVAGRAF is too strong or too weak, tell your doctor or pharmacist.
Following the initiation of your treatment with ADVAGRAF, frequent blood tests will be taken by your doctor to determine the correct dose and adjust the dose if needed.
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 the capsules immediately following removal from the blister. The capsules should be swallowed **whole** with a glass of water.
Do not chew and do not swallow the desiccant contained in the foil wrapper.
Do not use grapefruit or grapefruit juice while you are taking Advagraf.

If you take more ADVAGRAF than you should:
If you have taken too much ADVAGRAF, your doctor will amend your next dose.
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take / missed a dose of ADVAGRAF:
Do not take / receive a double dose to make up for forgotten individual doses.

Effects when treatment with ADVAGRAF is stopped:
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 ADVAGRAF, ask your doctor or pharmacist.

POSSIBLE SIDE EFFECTS:
ADVAGRAF can have side effects.
Not all side effects reported for ADVAGRAF are included in this leaflet. Should your general health worsen while taking ADVAGRAF, please consult your doctor, pharmacist or other health care professional for advice.
ADVAGRAF reduces your body's own defence mechanism to stop you rejecting your transplanted organ.

Cancerous and noncancerous tumours have been reported following ADVAGRAF treatment as a result of immunosuppression.
Severe effects have been reported, including allergic and anaphylactic reactions.
Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), agranulocytosis (a severely lowered number of white blood cells) and haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown) have been reported.
Your body will not be as good as usual at fighting infections. So if you are taking ADVAGRAF you may therefore get more infections than usual such as infections of the skin, mouth, stomach and intestines, lungs, urinary tract, and tuberculosis.

Possible side effects are listed according to the following categories:
Frequent side effects:

- Increased blood sugar, diabetes mellitus, increased potassium in the blood (which manifests as nausea, tiredness, muscle weakness, tingling sensation)
- Increased blood pressure
- Abnormal liver function tests
- Kidney problems
- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts
- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood (muscle weakness, confusion, decreased reflexes), fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts
- 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, changes in the lung tissue, collection of liquid around the lung, inflammation of the pharynx (throat), cough, flu-like symptoms
- Stomach problems such as inflammations or ulcers causing abdominal pain or diarrhoea, bleedings in the stomach, inflammations or ulcers in the mouth, collection of fluid in the belly, vomiting, abdominal pains, indigestion, constipation, flatulence, bloating, loose stools
- Bile duct disorders, changes in liver enzymes and function, 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 or back, 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
- Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- Diarrhoea, nausea
- Trembling, headache
- Difficulty in sleeping

Less frequent side effects:

- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- Changes in blood clotting, reduction in the number of all types of blood cells
- Dehydration, inability to urinate
- Abnormal blood test results: reduced protein or sugar, increased phosphate, increase of the enzyme lactate dehydrogenase
- 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, QT prolonged
- 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
- 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
- Muscular weakness
- Abnormal heart scan
- Liver failure
- Painful urination with blood in the urine
- Increase of fat tissue

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF ADVAGRAF:
Store all medicines out of reach of children.
Store at or below 30 °C.
Protect from light.
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.
Store in the original package in order to protect from moisture.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

PRESENTATION OF ADVAGRAF:
ADVAGRAF 0,5 mg is supplied in transparent PVC/PVDC aluminium blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50 and 100 prolonged-release capsules are available.
ADVAGRAF 1 mg is supplied in transparent PVC/PVDC aluminium blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50, 60 and 100 prolonged-release capsules are available.
ADVAGRAF 5 mg is supplied in transparent PVC/PVDC aluminium blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50 and 100 prolonged-release hard capsules are available.

IDENTIFICATION OF ADVAGRAF:
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 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 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.

REGISTRATION NUMBERS

South Africa:	**Namibia:**	**Kenya:**
24 Apr 2020, July 2021 (contact info)		Astellas

ADVAGRAF 0,5 mg:	42/34/0786	Reg No. 13/34/0225	CTD2276
ADVAGRAF 1 mg:	42/34/0787	Reg No. 13/34/0226	CTD2275
ADVAGRAF 5 mg:	42/34/0788	Reg No. 13/34/0227	CTD2277

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