PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

Graftac® 0,5 Prolonged Release (Capsules)

Graftac® 1 Prolonged Release (Capsules)

Graftac® 5 Prolonged Release (Capsules)

Tacrolimus

Each capsule of the GRAFTAC 0,5 PROLONGED RELEASE contains 53,650 mg lactose.

Each capsule of the GRAFTAC 1 PROLONGED RELEASE contains 107,300 mg lactose.

Each capsule of the GRAFTAC 5 PROLONGED RELEASE contains 536,500 mg lactose.

The printing ink used to mark the capsule contains trace amounts of soya lecithin (0,99 % of total printing ink composition).

GRAFTAC 0,5 PROLONGED RELEASE contains Tartrazine.

Read all of this leaflet carefully before you start taking GRAFTAC PROLONGED RELEASE

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.

- GRAFTAC PROLONGED RELEASE 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 is in this leaflet

1. What GRAFTAC PROLONGED RELEASE is and what it is used for
2. What you need to know before you take GRAFTAC PROLONGED RELEASE
3. How to take GRAFTAC PROLONGED RELEASE
4. Possible side effects
5. How to store GRAFTAC PROLONGED RELEASE
6. Contents of the pack and other information

1. What GRAFTAC PROLONGED RELEASE is and what it is used for

GRAFTAC PROLONGED RELEASE contains the active substance tacrolimus. It is an immunosuppressant and is a prolonged release formulation. GRAFTAC PROLONGED RELEASE is used to control your body's immune response, enabling your body to accept the transplanted organ.

You may also be given GRAFTAC PROLONGED RELEASE 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.

2. What you need to know before you take GRAFTAC PROLONGED RELEASE

Do not take GRAFTAC PROLONGED RELEASE

- If you are hypersensitive, (allergic) to tacrolimus or to any of the other, excipients of GRAFTAC PROLONGED RELEASE (listed in section 6).
- If you are allergic to any antibiotic belonging to the subgroup of macrolide antibiotics (e.g. erythromycin, clarithromycin, josamycin).

- If you are pregnant and breastfeeding.
- As GRAFTAC PROLONGED RELEASE may alter the metabolism of oral contraceptives, other forms of contraception should also be used.
- With live attenuated vaccines.
- With ciclosporin (another medicine used for the prevention of transplant organ rejection).
- With grapefruit juice.

Warnings and precautions

Take special care / Special care should be taken with GRAFTAC PROLONGED RELEASE:

GRAFTAC PROLONGED RELEASE contains the active substance tacrolimus presented in a prolonged-release formulation (delivers the dose over an extended period). GRAFTAC PROLONGED RELEASE is taken once daily and is not interchangeable with other existing medicines containing tacrolimus (immediate release formulations).

Tell your doctor if any of the following apply to you:

- If you are taking any medicines mentioned below under **'Other medicines and GRAFTAC PROLONGED RELEASE'**.
- 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 a pre-existing heart condition including QT prolongation (irregular conduction of the heart).
- If you have tuberculosis.

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 GRAFTAC PROLONGED RELEASE.

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 GRAFTAC PROLONGED RELEASE.

You should limit your exposure to the sun and UV (ultraviolet) light whilst taking GRAFTAC PROLONGED RELEASE. 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.

Patients treated with GRAFTAC PROLONGED RELEASE have been reported to have abnormality of some cells in the blood that is associated with a virus that is commonly known as Epstein-Barr Virus (EBV). If you are taking medicines that suppress the immune system, e.g. basiliximab or daclizumab with GRAFTAC PROLONGED RELEASE, this increases your risk of EBV-associated disorders.

If your doctor has told you that you are “EBV-Viral Capsid Antigen (VCA)-negative”, you could have an increased risk of developing immune system disorders where your white blood cells are increased. Your doctor will confirm if you are EBV-VCA negative prior to starting your treatment with GRAFTAC PROLONGED RELEASE. During your treatment, these levels will be monitored carefully.

The risk of secondary cancer with the use of GRAFTAC PROLONGED RELEASE is unknown.

If you are being treated with GRAFTAC PROLONGED RELEASE, the treatment may weaken your immune system and increase risk of developing infections (caused by e.g. bacteria, fungi, viruses).

Your doctor will need to confirm that you do not have tuberculosis before starting treatment with GRAFTAC PROLONGED RELEASE.

If you are being treated with GRAFTAC PROLONGED RELEASE, you will have an increased risk of developing a condition called posterior reversible encephalopathy syndrome (PRES). The symptoms of this condition include headache, changes in your mental condition/thought processes, seizures and visual disturbances. Let your doctor know if you experience any of these symptoms.

You are at increased risk for developing a condition called Pure Red Cell Aplasia (PRCA) when you are taking GRAFTAC PROLONGED RELEASE. PRCA is a rare disorder where there is a problem with how your red blood cells are made in your body and the amount of red blood cells are reduced. Signs that you have this disorder could appear as anaemia (a condition where you feel tired and weak, and you are pale).

Children and adolescents

The use of GRAFTAC PROLONGED RELEASE is not recommended in children and adolescents under 18 years.

Other medicines and GRAFTAC PROLONGED RELEASE

Always tell your health care provider if you are taking any other medicines. (This includes all complementary or traditional medicines.)

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

GRAFTAC PROLONGED RELEASE blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking GRAFTAC PROLONGED RELEASE, which may require interruption, an increase or a decrease in GRAFTAC PROLONGED

RELEASE 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 (cytomegalovirus, a common virus that happens in children and adults).
- 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).
- antidysrhythmic medicine(amiodarone) used to control dysrhythmia (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 GRAFTAC PROLONGED RELEASE.

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 (which prevent blood clots), or oral medicines for diabetes, while you take GRAFTAC PROLONGED RELEASE.

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

GRAFTAC PROLONGED RELEASE with food and drink

Do not use grapefruit (also as juice) while on treatment with GRAFTAC PROLONGED RELEASE, since it can affect its levels in the blood.

Pregnancy, breastfeeding and fertility

You should not use GRAFTAC PROLONGED RELEASE when you are pregnant or breastfeeding your baby.

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist, or other healthcare provider for advice before taking this medicine.

GRAFTAC PROLONGED RELEASE has a negative effect on male fertility in the form of reduced sperm counts and motility.

Driving and using machines

GRAFTAC PROLONGED RELEASE may cause visual and nervous system disturbance. If you are being treated with GRAFTAC PROLONGED RELEASE and experience the abovementioned effects, you should not drive a car or operate dangerous machines. This effect may be made worse when you take GRAFTAC PROLONGED RELEASE with alcohol.

It is not always possible to predict to what extent GRAFTAC PROLONGED RELEASE may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which GRAFTAC PROLONGED RELEASE affects them.

Important information about some of the ingredients of GRAFTAC PROLONGED RELEASE:

GRAFTAC PROLONGED RELEASE 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.

The printing ink used on GRAFTAC PROLONGED RELEASE capsules contains soya lecithin. If you are allergic to peanut or soya do not use this medicine.

GRAFTAC 0,5 PROLONGED RELEASE contains Tartrazine. This may cause allergic reactions.

3. How to take GRAFTAC PROLONGED RELEASE

Do not share medicines prescribed for you with any other person.

Always take GRAFTAC PROLONGED RELEASE exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

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.

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

GRAFTAC PROLONGED RELEASE is taken orally once daily in the morning. Take GRAFTAC PROLONGED RELEASE on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal. 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.

If you take more GRAFTAC PROLONGED RELEASE than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

Symptoms of overdosage may include kidney, nervous system and heart disturbances, an intolerance to a type of sugar called glucose, high blood pressure, and disorders of the electrolytes in the body (e.g., a higher than normal level of potassium in the blood). With overdosage, the immune system may be even more suppressed which may increase the risk for severe infections.

If you forget to take GRAFTAC PROLONGED RELEASE

If you have forgotten to take your GRAFTAC PROLONGED RELEASE capsules in the morning, take them as soon as possible on the same day.
Do not take / receive a double dose to make up for forgotten individual doses.

If you stop taking GRAFTAC PROLONGED RELEASE

Stopping your treatment with GRAFTAC PROLONGED RELEASE 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

GRAFTAC PROLONGED RELEASE can have side effects.
Not all side effects reported for GRAFTAC PROLONGED RELEASE are included in this leaflet.
Should your general health worsen or if you experience any untoward effects while taking GRAFTAC PROLONGED RELEASE, please consult your health care provider for advice.
GRAFTAC PROLONGED RELEASE reduces your body's own defence mechanism to stop rejection of your transplanted organ.
Cancerous and noncancerous tumours have been reported following GRAFTAC PROLONGED RELEASE treatment as a result of immunosuppression.
Severe effects have been reported, including allergic and anaphylactic reactions.
Your body will not be as good as usual at fighting infections. So if you are taking GRAFTAC PROLONGED RELEASE you may therefore get more infections than usual such as infections of the skin, mouth, stomach and intestines, lungs, urinary tract, and tuberculosis.

If any of the following happens, stop taking GRAFTAC PROLONGED RELEASE and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing.

- rash or itching.
- fainting.

These are all very serious side effects. If you have them, you may have had a serious reaction to GRAFTAC PROLONGED RELEASE. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

Serious frequent side effects:

• 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 less frequent side effects:

• 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.

• 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.

• 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, with symptoms such as chest pain (angina), fainting, vertigo or nausea, palpitations (feeling the heartbeat) and difficulty breathing.

Serious side effects - frequency is unknown:

• Opportunistic infections (bacterial, fungal, viral and protozoal): prolonged diarrhoea, 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 infections). You may have no symptoms, or you may feel sudden fever, rigors and sore throat.

• 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 GRAFTAC PROLONGED RELEASE.

• 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.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent side effects:

- Increased blood sugar, diabetes mellitus, increased potassium in the blood (which manifests as nausea, tiredness, muscle weakness, tingling sensation)
- Difficulty in sleeping
- Trembling, headache
- Increased blood pressure
- Liver function tests abnormal
- Diarrhoea, nausea
- 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 (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

Less frequent side effects:

- 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
- 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

Frequency unknown side effects:

- 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)
- Optic neuropathy
- Febrile neutropenia

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

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of GRAFTAC PROLONGED RELEASE.

Suspected adverse reactions can also be reported directly to the HCR via https://pvi1.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

5. How to store GRAFTAC PROLONGED RELEASE

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

- Store at or below 25 °C.
- Store in the original package (aluminium bag).
- Protect from light and moisture.
- Do not use after the expiry date stated on the carton / bottle label / blister.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What GRAFTAC PROLONGED RELEASE contains

The active substance is tacrolimus. Each prolonged-release capsule contains 0,5 mg, 1 mg or 5 mg tacrolimus.

The other ingredients are:

Capsule content (all capsules):

Ethylcellulose

Hypromellose type 2910

Lactose monohydrate

Magnesium stearate

Body Composition (all capsules):

Sunset yellow FCF (E110)

Allura red AC (E129)

Brilliant blue FCF (E133)

Titanium dioxide (E171)

Gelatine

Cap Composition (GRAFTAC 0,5 PROLONGED RELEASE):

Tartrazine (E102)

Titanium dioxide (E171)

Gelatine

Cap Composition (GRAFTAC 1 PROLONGED RELEASE):

Titanium dioxide (E171)

Gelatine

Cap Composition (GRAFTAC 5 PROLONGED RELEASE):

Erythrosin (E127)

Titanium dioxide (E171)

Gelatine

Imprinting ink (all capsules):

Shellac Glaze in ethanol

N-butyl alcohol

Allura Red AC Aluminium Lake (E129)

Brilliant Blue FCF Aluminium Lake (E133)

Isopropyl alcohol

Sunset Yellow FCF Aluminium Lake (E110)

Propylene glycol (E1520)

Lecithin (soya)

Simeticone

What GRAFTAC PROLONGED RELEASE looks like and contents of the pack

GRAFTAC 0,5 PROLONGED RELEASE (Capsules)

Light brown body and light-yellow cap with black print 0,5 mg.

GRAFTAC 1 PROLONGED RELEASE (Capsules)

Light brown body and white cap with black print 1 mg.

GRAFTAC 5 PROLONGED RELEASE (Capsules)

Light brown body and pink cap with black print 5 mg.

GRAFTAC PROLONGED RELEASE capsules, hard are packed into a PVC/PVDC aluminium blister wrapped in an aluminium bag (pouch) with a desiccant (silica gel).

Pack sizes:

The available pack sizes are 30’s and 60’s.

Not all pack sizes are marketed.

The blisters are packed together with the leaflet into the cardboard carton.

Holder of Certificate of Registration

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

2090

This leaflet was last revised in

23 January 2024

Registration numbers

GRAFTAC 0,5 PROLONGED RELEASE: 55/34/0854

GRAFTAC 1 PROLONGED RELEASE: 55/34/0855

GRAFTAC 5 PROLONGED RELEASE: 55/34/0856

Access to the corresponding Professional Information

Not applicable

[1]Company Reg. No.: 1990/001979/07