V4.0 (15.05.2025)

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS S4

Graftac® 0,5 mg (hard gelatine capsules)

Graftac® 1 mg (hard gelatine capsules)

Graftac® 5 mg (hard gelatine capsules)

tacrolimus

Each GRAFTAC 0,5 hard gelatine capsule contains 48,489 mg lactose monohydrate.

Each GRAFTAC 1 hard gelatine capsule contains 47,378 mg lactose monohydrate.

Each GRAFTAC 5 hard gelatine capsule contains 236,89 mg lactose monohydrate.

Read all of this leaflet carefully before you start taking GRAFTAC

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

1. What GRAFTAC is and what it is used for

GRAFTAC belongs to a group of medicines known as immunosuppressants. Following your organ transplant (e.g. liver, kidney, heart) your body's immune system will try to reject the new organ.

GRAFTAC is used to control your body's immune response enabling your body to accept the transplanted organ. GRAFTAC is often used in combination with other medicines that also suppress the immune system.

You may also be given GRAFTAC for an ongoing rejection of your transplanted liver, kidney, heart or other organ or if 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

Do not take GRAFTAC:

- If you are allergic to tacrolimus or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic (hypersensitive) to any antibiotic belonging to the subgroup of macrolide antibiotics (e.g erythromycin, clarithromycin, josamycin).
- If you are pregnant or breastfeeding your baby.
- GRAFTAC may alter the metabolism of oral contraceptives; other forms of contraception should be used.
- With live attenuated vaccines.
- With ciclosporin.
- With grapefruit juice.

Warnings and precautions:

Talk to your doctor or pharmacist before taking GRAFTAC:

- You will need to take GRAFTAC every day as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.
- Whilst you are taking GRAFTAC, your doctor may want to carry out a number of tests (including blood, urine, heart function, visual and neurological tests) from time to time. This is normal and will help your doctor to decide on the most appropriate dose of GRAFTAC for you.
- 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 GRAFTAC that you need to receive. If in doubt, please consult your doctor prior to taking any herbal products or remedies.
- If you have liver problems or have had a disease, which may have affected your liver, please tell your doctor as this may affect the dose of GRAFTAC that you receive.
- If you feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- If you have diarrhoea for more than one day, please tell your doctor, because it might be necessary to adapt the dose of GRAFTAC that you receive.
- If you have an alteration of the electrical activity of your heart called "QT prolongation".
- Limit your exposure to sunlight and UV light whilst taking GRAFTAC by wearing appropriate protective clothing and using a sunscreen with a high sun protection factor. This is because of the potential risk of malignant skin changes with immunosuppressive therapy.
- If you need to have any vaccinations, please inform your doctor beforehand. Your doctor will advise you on the best course of action.
- Patients treated with GRAFTAC have been reported to have an increased risk of developing lymphoproliferative disorders (see section 4). Ask your doctor for specific advice on these disorders.
- 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 you field of vision becomes restricted.

Other medicines and GRAFTAC:

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

GRAFTAC must not be taken simultaneously with ciclosporin.

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

Tell your doctor if you are taking or have recently taken any of the following medicines:

- Antifungal medicines and antibiotics (particularly so-called macrolide antibiotics) used to treat infections e.g., ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, and isavuconazole, erythromycin, clarithromycin, josamycin, and rifampicin.
- Letermovir, used to prevent illness caused by CMV (human cytomegalovirus).
- HIV protease inhibitors (e.g ritonavir, nelfinavir, saquinavir), the booster medicine cobicistat and combination tablets, used to treat HIV infection.
- HCV protease inhibitors (e.g., telaprevir, boceprevir and the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir), used to treat hepatitis C infection.
- Nilotinib and imatinib (used to treat certain cancers).
- Mycophenolic acid, used to suppress the immune system to prevent transplant rejection.
- Medicines for stomach ulcer and acid reflux (e.g., omeprazole, lansoprazole or cimetidine).
- Antiemetics, used to treat nausea and vomiting (e.g., metoclopramide).
- Magnesium-aluminium-hydroxide (antacid), used to treat heartburn.
- Hormone treatments with ethinylestradiol (e.g., the contraceptive pill) or danazol.
- Medicines for high blood pressure or heart problems such as nifedipine, nicardipine, diltiazem and verapamil.
- Anti-arrhythmic medicines (amiodarone) used to control arrhythmia (uneven beating of the heart).
- Medicines known as “statins” used to treat elevated cholesterol and triglycerides.
- The anti-epileptic medicines phenytoin or phenobarbital.

- The corticosteroids prednisolone and methylprednisolone.
- The anti-depressant nefazodone.
- 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 taking or need to take:

- Ibuprofen, amphotericin B or antivirals (e.g., aciclovir). These may worsen kidney or nervous system problems when taken together with GRAFTAC.
- Potassium supplements or certain diuretics (e.g., amiloride, triamterene, or spironolactone), certain painkillers (so-called NSAIDs, e.g., ibuprofen) anticoagulants or oral medication for diabetic treatment, while you take GRAFTAC.
- If you need to have any vaccinations, please inform your doctor beforehand. GRAFTAC may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective.

GRAFTAC with food and drink:

GRAFTAC should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal.
Do not use grapefruit or grapefruit juice while taking GRAFTAC since it can affect its levels in your blood.
Always take GRAFTAC capsule exactly as your doctor has told you.

Pregnancy and breastfeeding:

Do not take GRAFTAC if you are pregnant or breastfeeding your baby.
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking this medicine.
GRAFTAC is excreted into breast milk. Therefore, you should not breastfeed whilst receiving GRAFTAC.

Driving and using machines:

GRAFTAC may cause visual and nervous system disturbances.

If you are being treated with GRAFTAC and you are affected by you should not drive a car or operate dangerous machines. This effect may be made worse when you use GRAFTAC with alcohol.

It is not always possible to predict to what extent GRAFTAC 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 affects them.

GRAFTAC contains lactose monohydrate:

GRAFTAC contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take GRAFTAC

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

Always take GRAFTAC 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.

GRAFTAC should be taken twice 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 doses just after transplantation will generally be in the range of 0,02 to 0,40 mg per kg body weight per day depending on the transplanted organ.

Your dose depends on your general condition and on which other immunosuppressive medication you are taking. 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 GRAFTAC dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take and how often.

If you have the impression that the effect of GRAFTAC is too strong or too weak, tell your doctor or pharmacist.

- GRAFTAC is taken orally twice daily, usually in the morning and evening. You should generally take GRAFTAC on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal.
- The capsules should be swallowed whole with a glass of water.
- Take the hard capsules immediately following removal from the blister.
- Avoid grapefruit and grapefruit juice while taking GRAFTAC.
- Do not swallow the desiccant contained in the foil wrapper.

If you take more GRAFTAC than you should:

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

There is no specific antidote to overdosage and treatment must be symptomatic and supportive.

If you forget to take GRAFTAC:

Do not take a double dose to make up for a forgotten individual doses.

If you forget to take your capsule, take it as soon as you remember. If it is nearly time for the next dose, take it at the usual time.

If you stop taking GRAFTAC:

Stopping your treatment with GRAFTAC may increase the risk of rejection of your transplanted organ.

Do not stop taking your capsules even if you are feeling well, unless your doctor tells you.

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

4. Possible side effects

GRAFTAC can have side effects.

Not all side effects reported for GRAFTAC are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking GRAFTAC, please consult your doctor, pharmacist or other health care professional for advice.

GRAFTAC reduces your body's own defence mechanism to stop you rejecting your transplanted organ. Consequently, your body will not be as good as usual at fighting infections. So if you are taking GRAFTAC you may catch more infections than usual such as infections of the skin, mouth, stomach and intestines, lungs and urinary tract.

Severe side effects may occur, including the ones listed below.

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

- 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.
- 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).
- Cases of pure red cell aplasia (a very severe reduction in red blood cell counts) and haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown accompanied with tiredness) have been reported. 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, ankles, 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, altered mental status, seizures, and visual disturbances.
- *Torsades de Pointes*: change in the heart frequency that can be accompanied or not by symptoms, such as chest pain (angina), fainting, vertigo or nausea, palpitations (feeling the heartbeat) and difficulty breathing.
- Gastrointestinal perforation: strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- 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.
- Toxic epidermal necrolysis: erosion and blistering of skin or mucous membranes, red swollen skin that can detach in large parts of the body.
- 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.
- Insufficient function of your transplanted organ.

The following other side effects may also occur after receiving GRAFTAC:

Frequent side effects:

- Increased blood sugar, diabetes mellitus, increased potassium in the blood.
- Difficulty in sleeping.
- Trembling, headache.
- Increased blood pressure.
- Diarrhoea, nausea.

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

Less frequent side effects:

- Changes in blood clotting, reduction in all blood cell counts.
- 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.
- Blurring of the vision due to abnormality in the lens of the eye.
- 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.
- Dermatitis, burning sensation in the sunlight.
- Joint disorders.
- Inability to urinate, painful menstruation and abnormal menstrual bleeding.
- Failure of some organs, influenza-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.
- Small bleeds 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.
- Increased hairiness.
- Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer.
- Muscular weakness.

- Echocardiogram abnormal.
- Liver failure, narrowing of the bile vessel.
- Painful urination with blood in the urine.
- Increase of fat tissue.

Frequency not known side effects (cannot be estimated from the available data):

- Abnormality of the optic nerve (optic neuropathy).

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 or pharmacist. 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. Suspected side effects can also be reported directly to the Holder of the Certificate of Registration (HCR) via https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

5. How to store GRAFTAC

- **STORE ALL MEDICINES OUT OF REACH OF CHILDREN.**
- Store at or below 30 °C in the original package.
- Keep the blister in the outer carton.
- Use all the capsules within 12 months of opening the aluminium wrapping surrounding the blister.
- In-use blister pack should be stored at or below 25 °C.
- Take the capsule immediately after removing from the blister.
- Do not use GRAFTAC after the expiry date stated printed on the label or carton.

- 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 contains:

The active substance is tacrolimus.

Each GRAFTAC 0,5 hard gelatine capsule contains 0,511 mg tacrolimus monohydrate equivalent to 0,5 mg tacrolimus.

Each GRAFTAC 1 hard gelatine capsule contains 1,022 mg tacrolimus monohydrate equivalent to 1 mg tacrolimus.

Each GRAFTAC 5 hard gelatine capsule contains 5,11 mg tacrolimus monohydrate equivalent to 5 mg tacrolimus.

The other ingredients are:

Capsule contents:

Hypromellose (Methocel E6 LV)

Lactose monohydrate

Croscarmellose Sodium (Ac Di Sol)

Magnesium stearate

Hard gelatine capsule shell:

GRAFTAC 0,5 mg:

Gelatine

Titanium dioxide (E 171)

Sodium Lauryl Sulfate

Sorbitan Monolaurate

Yellow iron oxide (E 172)

GRAFTAC 1 mg:

Gelatine

Titanium dioxide (E 171)

Sodium Lauryl Sulfate

Sorbitan Monolaurate

Yellow iron oxide (E 172)

Red iron oxide (E 172)

Black iron oxide (E 172)

GRAFTAC 5 mg:

Gelatine

Titanium dioxide (E 171)

Sodium Lauryl Sulfate

Sorbitan Monolaurate

Red iron oxide (E 172)

What GRAFTAC looks like and contents of the pack:

GRAFTAC 0,5: White to off-white powder filled in size “4” capsule with white coloured opaque body and ivory coloured cap.

GRAFTAC 1: White to off-white powder filled in size “4” capsule with white coloured opaque body and light brown coloured cap.

GRAFTAC 5: White to off-white powder filled in size “3” capsule with white coloured opaque body and Swedish orange coloured cap.

The primary packaging for GRAFTAC blisters:

- PVC/ PE Laminate coated with PVdC (90 gsm), Clear.

- Hard Tempered Aluminium Foil (20 µ)

Blisters packed in triple laminated aluminium pouch containing molecular sieve packet.

The outer carton is a printed cardboard box.

Pack sizes:

7, 10, 14, 20, 28, 30, 50, 60, 90, 100 and 200 hard gelatine capsules.

Not all pack sizes are marketed.

Holder of Certificate of Registration

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

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Registration numbers

GRAFTAC 0,5: 43/34/1051

GRAFTAC 1: 43/34/1052

GRAFTAC 5: 43/34/1053

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