# PROFESSIONAL INFORMATION

**SCHEDULING STATUS:** S4

## 1. NAME OF THE MEDICINE:

Graftac® 0,5 Prolonged Release (Capsules)

Graftac® 1 Prolonged Release (Capsules)

Graftac® 5 Prolonged Release (Capsules)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each capsule of GRAFTAC 0,5 PROLONGED RELEASE contains 0,500 mg of tacrolimus equivalent to 0,511 mg of tacrolimus monohydrate.

Each capsule of GRAFTAC 1 PROLONGED RELEASE contains 1,000 mg of tacrolimus equivalent to 1,022 mg of tacrolimus monohydrate.

Each capsule of GRAFTAC 5 PROLONGED RELEASE contains 5,000 mg of tacrolimus equivalent to 5,112 mg of tacrolimus monohydrate.

**Excipients with known effect:**

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).

For full list of excipients, see Section 6.1.

**3. PHARMACEUTICAL FORM:**

Prolonged release hard capsule.

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.

**4. CLINICAL PARTICULARS:**

**4.1. Therapeutic indications:**

Prophylaxis of transplant rejection in adult kidney or liver allograft recipients.

Treatment of allograft rejection resistant to treatment with other immunosuppressive medicines in adult patients.

**4.2 Posology and method of administration:**

Inadvertent, unintentional, or unsupervised switching between immediate and prolonged release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including under- or over immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take

place under the close supervision of a transplant specialist. Following conversion to any alternative formulation, therapeutic medicine monitoring must be performed, and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

**General statement**

The recommended initial dosages presented below are intended to act solely as a guideline. GRAFTAC PROLONGED RELEASE is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative transplant period. The GRAFTAC PROLONGED RELEASE dose may vary depending upon the immunosuppressive regimen chosen. GRAFTAC PROLONGED RELEASE dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

**Posology:**

**Duration of dosing:**

To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the duration of oral therapy can be given.

**Dosage recommendations - Prophylaxis of Transplant Rejection: *Kidney transplantation:***

*Initial dose (primary immunosuppression):*

Oral GRAFTAC PROLONGED RELEASE therapy should commence at a dose of 0,20 to 0,30 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery.

*Maintenance therapy:*

GRAFTAC PROLONGED RELEASE doses are usually reduced during maintenance therapy. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to GRAFTAC PROLONGED RELEASE-based dual therapy. Post- transplant improvement in the

condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate dose adjustment.

**Dosage recommendations - Prophylaxis of Transplant Rejection: *Liver transplantation:***

*Initial dose (primary immunosuppression):*

Oral GRAFTAC PROLONGED RELEASE therapy should commence at a dose of 0,10 to 0,20 mg/kg/day administered once daily in the morning. Administration should commence approximately 12 to 18 hours after the completion of surgery.

*Maintenance therapy:*

GRAFTAC PROLONGED RELEASE doses are usually reduced during maintenance therapy. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to GRAFTAC PROLONGED RELEASE monotherapy. Post- transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate dose adjustment.

**Dosage recommendations - Conversion of immediate release formulation tacrolimus treated patients to GRAFTAC PROLONGED RELEASE:**

Allograft transplant patients maintained on twice daily tacrolimus immediate release formulation dosing requiring conversion to once daily GRAFTAC PROLONGED RELEASE may be converted on a 1:1 (mg/mg) total daily dose basis. GRAFTAC PROLONGED RELEASE should be administered in the morning. Following conversion, tacrolimus trough levels should be monitored, and if necessary, dose adjustments made to maintain similar systemic exposure.

**Dosage recommendations - Rejection therapy:**

Increased doses of tacrolimus, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g., pronounced adverse reactions) the dose of GRAFTAC PROLONGED RELEASE may need to be reduced.

For information on conversion from ciclosporin to GRAFTAC PROLONGED RELEASE, see below under DOSAGE ADJUSTMENTS IN SPECIFIC PATIENT POPULATIONS.

- ***Kidney and liver transplantation:***

For conversion from other immunosuppressants to once daily GRAFTAC PROLONGED RELEASE, treatment should begin with the initial oral dose recommended for primary immunosuppression.

- ***Other allografts transplantation:***

No data for GRAFTAC PROLONGED RELEASE for lung-transplanted, pancreas-transplanted and intestine-transplanted patients are available.

**DOSAGE ADJUSTMENTS IN SPECIFIC PATIENT POPULATIONS:**

***Patients with liver impairment:***

Dose reduction may be necessary in patients with severe liver impairment in order to maintain the blood trough levels within the recommended target range.

***Patients with kidney impairment:***

As the pharmacokinetics of tacrolimus are unaffected by renal function, no dose adjustment should be required. However, owing to the nephrotoxic potential of GRAFTAC PROLONGED RELEASE careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

***Race:***

In comparison to Caucasians, Black patients may require higher GRAFTAC PROLONGED RELEASE doses to achieve similar trough levels.

***Elderly patients:***

There is no evidence currently available to indicate that dosing should be adjusted in elderly patients.

***Paediatric patients:***

The safety and efficacy of GRAFTAC PROLONGED RELEASE in children under 18 years of age have not been established. Limited data are available but no recommendation on a dosage can be made.

**Conversion from ciclosporin to GRAFTAC PROLONGED RELEASE:**

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. GRAFTAC PROLONGED RELEASE therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12 to 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Various assays have been used to measure blood or plasma levels of GRAFTAC PROLONGED RELEASE. Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting medicines and the post-transplant time interval. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Whole blood specimens should be collected into tubes containing ethylene diamine tetra acetic acid (EDTA) anticoagulant. Heparin anticoagulation is not recommended because of the tendency to form clots on storage. Samples that are not analysed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer, they should be deep frozen at -20°C for up to 12 months.

Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Blood trough levels for tacrolimus should be drawn approximately 24 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As GRAFTAC PROLONGED RELEASE is a medicine with low clearance, adjustments to the GRAFTAC PROLONGED RELEASE dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations. Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

In clinical practice, whole blood trough levels have generally been in the range of 5 to 20 ng/ml in liver transplant recipients and 10 to 20 ng/ml in kidney transplant patients in the early post-transplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5 to 15 ng/ml in liver, kidney and heart transplant recipients.

**Method of administration:**

It is recommended that the oral daily dose of GRAFTAC PROLONGED RELEASE be administered once daily in the morning.

GRAFTAC PROLONGED RELEASE capsules should be taken immediately following removal from the blister. The capsules should be swallowed with fluid (preferably) water.

GRAFTAC PROLONGED RELEASE should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. If a patient recognises that he has forgotten to take the morning dose, he should take his dose as soon as possible on the same day. He should not take a double dose the next morning.

**4.3. Contraindications:**

- Hypersensitivity to tacrolimus, or to any of the excipients listed in section 6.1.
- Hypersensitivity to other macrolides
- Pregnancy and lactation (see section 4.6)
- As GRAFTAC PROLONGED RELEASE may alter the metabolism of oral contraceptives, other forms of contraception should be used.
- Concomitant administration of live attenuated vaccines.
- Concomitant administration with ciclosporin.
- Concomitant use with grapefruit juice.

**4.4. Special warnings and precautions for use:**

**Prolonged release formulations of tacrolimus such as GRAFTAC PROLONGED RELEASE are not interchangeable with immediate-release formulations of tacrolimus, without careful monitoring and supervision by a transplant specialist.**

GRAFTAC PROLONGED RELEASE therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources. GRAFTAC PROLONGED RELEASE should only be prescribed and changes in immunosuppressive therapy, should only be initiated by medical practitioners experienced in immunosuppressive therapy and the management of transplant patients. The medical practitioner responsible for maintenance therapy should have complete information requisite for the follow-up of the patient. Dose and/or blood level adjustment, should only be undertaken by the transplant centre responsible for the transplant patient. Patients should be thoroughly controlled. In particular, during the first month’s post-transplant, close monitoring of the patient is required.

During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels,

electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

When substances with a potential for interaction (see section 4.5) - particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampicin, rifabutin and anti-epileptic medicine) – are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the GRAFTAC PROLONGED RELEASE dose as appropriate in order to maintain similar tacrolimus exposure.

Herbal preparations containing St. John's Wort *(Hypericum perforatum*), or other herbal preparations should be avoided when taking GRAFTAC PROLONGED RELEASE due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity (see section 4.5).

The combined administration of ciclosporin and tacrolimus should be avoided, and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.3 and 4.5).

High potassium intake or potassium-sparing diuretics should be avoided (see section 4.5).

Certain combinations of tacrolimus with medicines known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).
Nephrological adverse events can occur throughout the entire treatment period and, in case of kidney transplant recipients, should be distinguished from symptoms of kidney graft rejection.

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

**Gastrointestinal disorders:**

Gastrointestinal perforation has been reported in patients treated with tacrolimus. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur. Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.

**Cardiac disorders:**

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g., initially at 3 months and then at 9-12 months). If abnormalities develop, dose reduction of GRAFTAC PROLONGED RELEASE, or change of treatment to another immunosuppressive medicine should be considered. Tacrolimus may prolong the QT interval and may cause *Torsades de Pointes*. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradydysrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see section 4.5).

**Lymphoproliferative disorders and malignancies:**

Patients treated with tacrolimus have been reported to develop Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders (see section 4.8). A combination of immunosuppressives such as antilymphocytic antibodies (e.g., basiliximab, daclizumab) given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with GRAFTAC PROLONGED RELEASE. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is *per se* not indicative of lymphoproliferative disease or lymphoma.

The risk of secondary cancer with the use of GRAFTAC PROLONGED RELEASE is unknown (see section 4.8).

Owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor during treatment with GRAFTAC PROLONGED RELEASE.

**Infections including opportunistic infections:**

Patients treated with immunosuppressants, including GRAFTAC PROLONGED RELEASE are at increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal) such as BK virus associated nephropathy and John Cunningham (JC) virus associated progressive multifocal leukoencephalopathy (PML). Patients are also at an increased risk of infections with viral hepatitis (for example, hepatitis B and C reactivation and de novo infection, as well as hepatitis E, which may become chronic). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that medical practitioners should consider in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or

neurological symptoms. Prevention and management should be in accordance with appropriate clinical guidance.

Tuberculosis must be excluded prior to GRAFTAC PROLONGED RELEASE treatment.

**Posterior reversible encephalopathy syndrome (PRES):**

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus 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 and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

**Eye disorders:**

Eye disorders, sometimes progressing to loss of vision, have been reported in patients treated with tacrolimus. Some cases have reported resolution on switching to alternative immunosuppression. Patients should be advised to report changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, and in such cases, prompt evaluation is recommended with referral to an ophthalmologist as appropriate.

**Pure Red Cell Aplasia:**

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA.

**Special populations:**

There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g., re-transplantation, evidence of panel reactive antibodies, PRA).
Dose reduction may be necessary in patients with severe liver impairment (see section 4.2).
GRAFTAC PROLONGED RELEASE is not recommended for use in children below 18 years due to limited data on safety and/or efficacy.

**Excipients**

GRAFTAC PROLONGED RELEASE capsules contains lactose. This should be taken into account in patients with diabetes mellitus.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
The printing ink used to mark GRAFTAC PROLONGED RELEASE capsules contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using GRAFTAC PROLONGED RELEASE.

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

**4.5. Interaction with other medicines and other forms of interaction:**

Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.
It is strongly recommended to closely monitor tacrolimus blood levels, as well as QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

**CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels:**

Strong interactions with antifungal medicines such as ketoconazole, fluconazole, itraconazole, voriconazole and isavuconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir, and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir), or the CMV antiviral letermovir, the pharmacokinetic enhancer cobicistat, and the tyrosine kinase inhibitors nilotinib and imatinib. Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, nefazodone and (Chinese) herbal remedies containing extracts of *Schisandra sphenanthera*.

Potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethindrone, quinidine, tamoxifen, (triacetyl) oleandomycin.

Grapefruit juice may increase the blood level of tacrolimus and should therefore be avoided.

Lansoprazole and ciclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

**Other interactions potentially leading to increased tacrolimus blood levels:**

Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics).

Other potential interactions that may increase systemic exposure of tacrolimus include prokinetic medicines (such as metoclopramide and cisapride), cimetidine and magnesium-aluminium-hydroxide.

**CYP3A4 inducers potentially leading to decreased tacrolimus blood levels:**

Strong interactions with rifampicin, phenytoin, St. John's Wort (*Hypericum perforatum*) which may require increased tacrolimus doses. Significant interactions may occur with phenobarbital. Maintenance doses of corticosteroids may reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.

Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

**Effect of tacrolimus on the metabolism of other medicines:**

Tacrolimus is a known CYP3A4 inhibitor; thus, concomitant use of tacrolimus with medicines known to be metabolised by CYP3A4 may affect the metabolism of such medicines.

The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is contraindicated (see sections 4.3 and 4.4).

Tacrolimus may increase the blood level of phenytoin.

As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.

Limited knowledge of interactions between tacrolimus and statins is available. The pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.

Tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

Mycophenolic acid. Caution should be exercised when switching combination therapy from ciclosporin, which interferes with enterohepatic recirculation of mycophenolic acid, to tacrolimus, which is devoid of this effect, as this might result in changes of mycophenolic acid exposure. Medicines which interfere with mycophenolic acid's enterohepatic cycle have potential to reduce the plasma level and efficacy of mycophenolic acid. Therapeutic monitoring of mycophenolic acid may be appropriate when switching from ciclosporin to tacrolimus or vice versa.

**Other interactions leading to clinically detrimental effects:**

Concurrent use of tacrolimus with medicines known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, NSAIDs, ganciclovir or aciclovir).

Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.

As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone) should be avoided (see section 4.4).

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided (see section 4.3).

**4.6 Fertility, pregnancy, and breastfeeding:**

**Pregnancy:**

GRAFTAC PROLONGED RELEASE is contraindicated in pregnancy (see section 4.3). In animal studies (rats and rabbits), tacrolimus has been shown to be teratogenic at doses that also demonstrated maternal toxicity. Tacrolimus is able to cross the placenta. The possibility of pregnancy should therefore be excluded before initiating GRAFTAC PROLONGED RELEASE therapy.

**Breastfeeding:**

Tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breastfeed whilst receiving GRAFTAC PROLONGED RELEASE.

**Fertility:**

A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.

**4.7. Effects on ability to drive and use machines:**

Tacrolimus may cause visual and neurological disturbances. Patients treated with GRAFTAC PROLONGED RELEASE who are affected by such disorders should not drive a car or operate dangerous machines. This effect may be enhanced when GRAFTAC PROLONGED RELEASE is given together with alcohol.

**4.8. Undesirable effects:**

The adverse reactions profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medicines.

The most frequent adverse reactions are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia.

**Blood and the lymphatic system disorders:**

***Frequent*:** anaemia, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leukocytosis

***Less frequent*:** coagulopathies, pancytopenia, neutropenia, abnormal coagulation and bleeding analyses, thrombotic thrombocytopenic purpura, hypoprothrombinaemia, thrombotic microangiopathy

***Frequency unknown*:** pure red cell aplasia, agranulocytosis, haemolytic anaemia

**Immune system disorders:**

Allergic and anaphylactoid reactions may occur in patients receiving tacrolimus (see section 4.4)

**Endocrine disorders:**

***Less frequent*:** hirsutism

**Metabolism and nutrition disorders:**

***Frequent*:** diabetes mellitus, hyperglycaemic conditions, hyperkalaemia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia, anorexia

***Less frequent:*** dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia

**Psychiatric disorders:**

***Frequent*:** insomnia, confusion and disorientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare

***Less frequent:*** psychotic disorder

**Nervous system disorders:**

***Frequent*:** headache, tremor, nervous system disorders, seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dysaesthesias, writing impaired

***Less frequent:*** encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, speech and language abnormalities, paralysis and paresis, amnesia, hypertonia, myasthenia

**Eye disorders:**

***Frequent*:** eye disorders, vision blurred, photophobia

***Less frequent:*** cataract, blindness

***Frequency unknown:*** optic neuropathy

**Ear and labyrinth disorders:**

***Frequent:*** tinnitus

***Less frequent:*** hypoacusis, deafness neurosensory, hearing impaired

**Cardiac disorders:**

***Frequent*:** ischaemic coronary artery disorders, tachycardia

***Less frequent*:** heart failures, ventricular dysrhythmias and cardiac arrest, supraventricular dysrhythmias, cardiomyopathies, ventricular hypertrophy, palpitations, pericardial effusion, Torsades de Pointes, abnormal ECG investigations, abnormal heart rate and pulse investigations, abnormal echocardiogram, QT prolongation.

**Vascular disorders:**

***Frequent:*** hypertension, thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders

***Less frequent:*** venous thrombosis deep limb, shock, infarction

**Respiratory, thoracic and mediastinal disorders:**

***Frequent:*** parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations

***Less frequent:*** respiratory failures, respiratory tract disorders, asthma, acute respiratory distress syndrome

**Gastrointestinal disorders:**

***Frequent:*** diarrhoea, nausea, gastrointestinal signs and symptoms, vomiting, gastrointestinal and abdominal pains, gastrointestinal inflammatory conditions, gastrointestinal haemorrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and distension, loose stools

***Less frequent*****:** acute and chronic pancreatitis, ileus paralytic, gastro-oesophageal reflux disease, impaired gastric emptying, pancreatic pseudocyst, subileus, peritonitis, increased blood amylase

**Hepatobiliary disorders:**

***Frequent:*** bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice, abnormal liver function tests

***Less frequent*****:** veno-occlusive liver disease, hepatic artery thrombosis, hepatic failure

**Skin and subcutaneous tissue disorders:**

***Frequent:*** rash, pruritus, alopecias, acne, sweating increased

***Less frequent:*** dermatitis, photosensitivity, toxic epidermal necrolysis (Lyell's syndrome), Stevens Johnson syndrome

**Musculoskeletal and connective tissue disorders:**

***Frequent:*** arthralgia, back pain, muscle spasms, pain in extremity

***Less frequent:*** joint disorders, mobility decreased

**Renal and urinary disorders:**

***Frequent:*** renal impairment, renal failure, renal failure acute, nephropathy toxic, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms

***Less frequent:*** haemolytic uraemic syndrome, anuria, nephropathy, cystitis haemorrhagic

**Reproductive system and breast disorders:**

***Less frequent:*** dysmenorrhoea and uterine bleeding

**General disorders and administration site conditions:**

***Frequent:*** febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed

***Less frequent:*** influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance, fall, ulcer, chest tightness, thirst, fat tissue increased

***Frequency unknown:*** febrile neutropenia

**Investigations:**

***Frequent:*** liver function tests abnormal, blood alkaline phosphatase increased, weight increased

***Less frequent:*** amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactase dehydrogenase increased, echocardiogram abnormal, electrocardiogram QT prolonged

**Injury, poisoning and procedural complications:**

***Frequent:*** primary graft dysfunction

Medication errors, including inadvertent, unintentional, or unsupervised substitution of immediate or prolonged release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).

**Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after authorisation of the medicine[~~s~~] is important. It allows continued monitoring of the benefit/risk balance of the medicines. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via the website: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

**4.9. Overdose:**

Experience of overdosage is limited.

Earlier clinical experience (when initial induction doses were 2 or 3 times greater than those currently recommended) suggested that symptoms of overdosage may include renal, neurological and cardiac disturbances, glucose intolerance, hypertension and electrolyte disorders (e.g., hyperkalaemia). Over-immunosuppression may increase the risk for severe infections.

Liver function clearly influences all pre- and post-operative pharmacokinetic variables. Patients with failing liver grafts or those switched from other immunosuppressive therapy to GRAFTAC PROLONGED RELEASE should be monitored carefully to avoid overdosage.

No specific antidote to GRAFTAC PROLONGED RELEASE therapy is available. If overdosage occurs general supportive measures and symptomatic treatment should be conducted.
Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that GRAFTAC PROLONGED RELEASE will not be dialysable.

In isolated patients with very high plasma concentrations of tacrolimus, haemofiltration and haemodiafiltration have been reported to considerably decrease the tacrolimus levels. In cases of oral intoxication, the use of absorbents (such as activated charcoal) may be helpful.

## 5. PHARMACOLOGICAL PROPERTIES:

### 5.1 Pharmacodynamic properties:

***Category and class:*** A.34 Other (Immuno-suppressive macrolide lactone)

***Pharmacotherapeutic group:*** Immunosuppressants calcineurin inhibitors

***ATC code:*** L04AD02

***Mechanism of action***

At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The

FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.

Tacrolimus has immunosuppressive properties. In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.

**5.2. Pharmacokinetic properties:**

**Absorption:**

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Tacrolimus in GRAFTAC PROLONGED RELEASE is a prolonged release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to maximum blood concentration ($C_{max}$) of approximately 2 hours ($t_{max}$).

Absorption is variable and the mean oral bioavailability of tacrolimus is in the range of 20 % - 25 % (individual range in adult patients 6 % - 43 %). The oral bioavailability of tacrolimus was reduced when it was administered after a meal. Both the rate and extent of absorption of tacrolimus were reduced when administered with food.

Bile flow does not influence the absorption of tacrolimus. A strong correlation exists between AUC and whole blood trough levels at steady state for tacrolimus. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

**Distribution:**

In man, the disposition of tacrolimus after intravenous infusion may be described as biphasic.

In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is highly bound (> 98,8 %) to plasma proteins, mainly to serum albumin and alpha-1-acid glycoprotein.

Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1300 L (healthy subjects). Corresponding data based on whole blood averaged 47,6 L.

**Biotransformation:**

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4. Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to the pharmacological activity of tacrolimus.

**Excretion:**

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2,25 L/h. In adult liver, kidney and heart transplant patients, values of 4,1 L/h, 6,7 L/h and 3,9 L/h, respectively, have been observed. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism, are considered to be responsible for the higher clearance rates observed following transplantation.

The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours.

Following intravenous and oral administration of $^{14}C$-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2 % of the radioactivity was eliminated in the urine. Less than 1 % of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

**5.3 Preclinical safety data**

Not applicable.

**6. PHARMACEUTICAL PARTICULARS:**

**6.1 List of excipients:**

**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

**6.2. Incompatibilities**

Tacrolimus is not compatible with PVC (polyvinylchloride). Tubing, syringes and other equipment used to prepare a suspension of GRAFTAC PROLONGED RELEASE capsule contents must not contain PVC.

**6.3. Shelf life**

24 months

**6.4. Special precautions for storage**

Store at or below 25 °C.

Store in the original package (aluminium bag).

Protect from light and moisture.

### 6.5. Nature and contents of container

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

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

**Pack sizes:**

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

Not all pack sizes may be marketed.

### 6.6. Special precautions for disposal and other handling

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

2090

## 8. REGISTRATION NUMBERS

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

GRAFTAC 1 PROLONGED RELEASE: 55/34/0855

GRAFTAC 5 PROLONGED RELEASE: 55/34/0856

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 January 2024

## 10. DATE OF REVISION OF THE TEXT

Not applicable.

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