Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

V2.0 (11/10/2022)

CLEAN PROPOSED PROFESSIONAL INFORMATION [PRODUCT NAME]

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE:

[PRODUCT NAME]® 0,5 mg (hard gelatine capsules)

[PRODUCT NAME]® 1 mg (hard gelatine capsules)

[PRODUCT NAME]® 5 mg (hard gelatine capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each [PRODUCT NAME] 0,5 hard gelatine capsule contains 0,511 mg tacrolimus monohydrate equivalent to 0,5 mg tacrolimus.

Each [PRODUCT NAME] 1 hard gelatine capsule contains 1,022 mg tacrolimus monohydrate equivalent to 1 mg tacrolimus.

Each [PRODUCT NAME] 5 hard gelatine capsule contains 5,11 mg tacrolimus monohydrate equivalent to 5 mg tacrolimus.

Excipients with known effect:

[PRODUCT NAME] 0,5 contains sugar (lactose monohydrate 48,489 mg)

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

[PRODUCT NAME] 1 contains sugar (lactose monohydrate 47,378 mg)

[PRODUCT NAME] 5 contains sugar (lactose monohydrate 236,89 mg)

For full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM:

Hard gelatine capsule.

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

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

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

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

Primary immunosuppression in liver and kidney allograft recipients and liver, kidney or heart allograft rejection resistant to conventional immunosuppressive regimens.

4.2 Posology and method of administration

Inadvertent, unintentional or unsupervised switching between immediate- and prolonged release formulations of tacrolimus such as [PRODUCT NAME] is unsafe. This can lead to graft rejection or increased incidence of side effects, including under- or overimmunosuppression, 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.

Absorption of orally administered tacrolimus in the immediate postoperative period in heart transplant patients is problematic and creates difficulties in designing a suitable dosing regimen. Therefore initiation of [PRODUCT NAME] therapy via the intravenous route and conversion to oral dosing, when possible, or initiating [PRODUCT NAME] orally following antibody induction therapy are the two preferable options for use of [PRODUCT NAME] in heart transplant patients.

General statement:

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

The dosage recommendations given below are intended to act as a guideline. [PRODUCT NAME] doses should be adjusted according to individual patient requirements.

If the clinical condition of the patient allows oral dosing, administration of oral [PRODUCT NAME] should start as soon as practicable. In some liver transplantation patients, therapy has commenced orally by administering the capsule contents suspended in water via an intranasal gastric tube.

[PRODUCT NAME] is normally administered together with other immunosuppressive agents. In isolated cases, successful maintenance therapy with [PRODUCT NAME] alone has also been described. [PRODUCT NAME] should not be given together with ciclosporin (see section 4.3). If allograft rejection or adverse events occur, alteration in the immunosuppressive regimen should be considered.

Maintenance therapy in liver and kidney transplant recipients (adults and children) – general considerations:

Continuous immunosuppression with [PRODUCT NAME] is recommended to maintain graft survival. If progression of disease occurs (e.g., signs of acute rejection), alteration of the immunosuppressive regimen should be considered. Increase in the number of corticosteroids, introduction of short courses of monoclonal antibodies and increase in the dose of [PRODUCT NAME] have all been used to manage rejection episodes.

If signs of toxicity are noted, the dose of [PRODUCT NAME] should be reduced. Patients should be instructed not to decrease the dose without the consent of the treating physician.

During the course of the post-transplant improvement of the patient, it is likely that the pharmacokinetics of [PRODUCT NAME] may be altered, requiring adjustment of the [PRODUCT NAME] dose.

Primary immunosuppression - adult patients:

Liver transplantation:

Initially, an oral dose in a range from 0,10 to 0,20 mg/kg/day should be administered in two divided doses. Initial oral doses have been administered in a range from 0,02 to 0,30 mg/kg/day.

Kidney transplantation:

Initial administration:

Initially, an oral dose in a range from 0,15 – 0,40 mg/kg/day should be administered in two divided doses. If the clinical condition of the patient does not allow for oral dosing, then an initial intravenous dose of 0,05 – 0,10 mg/kg/24 h should be administered as a continuous infusion within the first 24 hours after the completion of surgery. Patients should be converted from intravenous to oral medication as soon as the individual circumstances permit.

Primary immunosuppression dose levels – paediatric patients: (see section 4.4)

Paediatric patients generally require doses 1½ to 2 times higher than the recommended adult doses to achieve the same blood levels. Experience with initial oral administration in paediatric patients is limited.

Liver and kidney transplantation:

An initial dose of 0,30 mg/kg/day for liver and kidney transplantation should be administered in two divided doses. If the dose cannot be given orally, an initial intravenous dose of 0,05 mg/kg/day for liver transplantation or 0,10 mg/kg/day for kidney transplantation should be administered as a continuous 24-hour infusion.

Maintenance therapy with [PRODUCT NAME] in liver or kidney transplant recipients:

It is necessary to continue immunosuppression with oral [PRODUCT NAME] to maintain graft survival. Dosage recommendations should be based on individual patient experience (see introductory remarks above). There is a trend towards the use of lower doses of [PRODUCT NAME] during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability.

Rescue therapy with [PRODUCT NAME]:

In patients experiencing rejection episodes that are unresponsive to conventional immunosuppressive therapy, [PRODUCT NAME] treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.

The combined administration of ciclosporin and [PRODUCT NAME] is not recommended as [PRODUCT NAME] may increase the half-life of ciclosporin and exacerbate any toxic effects (see section 4.5).

Therefore, care should be taken when converting patients from ciclosporin- to [PRODUCT NAME] -based therapy. It is recommended that ciclosporin blood levels are monitored prior to the administration of [PRODUCT NAME]. The most appropriate time to initiate [PRODUCT NAME] therapy should be based upon information on ciclosporin blood levels and the clinical condition of the patient.

Dosing may be delayed in the presence of elevated ciclosporin levels e.g., in patients experiencing renal failure. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin may be affected.

Heart allograft rejection:

An initial oral dose of 0,30 mg/kg/day should be administered in two divided doses (e.g., morning and evening). If the clinical condition of the patient prevents oral administration, an intravenous dose of 0,05 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustments in specific patient populations:

Patients with liver impairment:

A dose reduction may be necessary in patients with pre- and/or postoperative impairment, e.g., early graft dysfunction.

Patients with kidney impairment:

No adjustment in dose is regarded as necessary on pharmacokinetic principles. However, careful monitoring of renal function, including serial creatinine estimations, calculations of creatinine clearance and monitoring of urine output, is recommended.

Race:

In comparison to Caucasians, Black patients may require higher [PRODUCT NAME] doses to achieve similar trough levels.

Elderly patient:

There is no evidence presently available to suggest that doses should be altered in elderly patients.

Paediatric patients:

The safety and efficacy of [PRODUCT NAME] in children under 18 years of age have not yet been established. Limited data are available but no recommendation on a dosage can be made (see section 4.4).

Conversion from ciclosporin to [PRODUCT NAME]:

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. [PRODUCT NAME] 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, [PRODUCT NAME] 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 [PRODUCT NAME]. 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 ºC for up to 12 months.

[PRODUCT NAME] whole blood trough levels should be monitored periodically during maintenance therapy. The frequency of blood level monitoring should be based on clinical needs, but in general, because of its long half-life, it is unnecessary to measure blood levels on a daily basis. Medicine level monitoring (TDM) is recommended during the early post-transplantation period, following dose adjustment, after switching from another immunosuppressive regimen, and following co-administration of medicines which are likely to lead to interactions.

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

Clinical experience suggests that the majority of patients can be successfully managed if the blood concentrations of [PRODUCT NAME] are maintained below 25 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood level concentrations. If the blood levels are below the limit of quantification of the assay and the patient's clinical condition is satisfactory, then the dose should not be adjusted.

Method of administration:

It is recommended that the oral daily dose should be taken in two divided doses. The capsules should be swallowed with fluid, preferably water. Based on pharmacokinetic considerations, the capsules should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal to achieve maximal absorption (see section 4.5 and 5.2).

The capsules should be taken out of the blister only immediately before intake. After opening the aluminium wrapper, the capsules from the blisters must be used within 12 months. Patients should be cautioned not to swallow the desiccant contained within the aluminium wrapper.

Duration of dosing:

To suppress graft rejection, the capsules normally have to be taken continuously. Therefore, no limitation of duration can be given.

4.3. Contraindications:

- Hypersensitivity to tacrolimus, or other macrolides.
- Hypersensitivity to any of the excipients listed in section 6.1.

- Pregnancy and lactation (see section 4.6).
- As [PRODUCT NAME] 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 are not interchangeable with immediate-release formulations of tacrolimus, without careful monitoring and supervision by a transplant specialist.

[PRODUCT NAME] therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources. [PRODUCT NAME] 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 months post-transplant, close monitoring of the patient is required.

[PRODUCT NAME] is not recommended for use in children below 18 years due to limited data on safety and/or efficacy.

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate or prolonged-release tacrolimus formulations have been observed. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under- or overexposure 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 (see sections 4.2 and 4.8).

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.

Substances with potential for interaction

Inhibitors or inducers of CYP3A4 should only be co-administered with tacrolimus after consulting a transplant specialist, due to the potential for drug interactions resulting in serious adverse reactions including rejection or toxicity (see section 4.5).

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

CYP3A4 inhibitors

Concomitant use with CYP3A4 may increase tacrolimus blood levels, which could lead to serious adverse reactions, including nephrotoxicity and QT prolongation. It is recommended that concomitant use of strong CYP3A4 inhibitors (such as ritonavir, telaprevir, boceprevir, cobicistat, ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin or josamycin) with [PRODUCT NAME] should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of coadministration, under the supervision of a transplant specialist, to adjust the [PRODUCT NAME] dose if appropriate in order to maintain similar tacrolimus exposure. Renal function, ECG including the QT interval, and the clinical condition of the patient should also be closely monitored.
Dose adjustment needs to be based upon the individual situation of each patient. An immediate dose reduction at the time of treatment initiation may be required (see section 4.5).
Similarly, discontinuation of CYP3A4 inhibitors may affect the rate of metabolism of [PRODUCT NAME], thereby leading to subtherapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

CYP3A4 inducers

Concomitant use with CYP3A4 inducers may decrease tacrolimus blood levels, potentially increasing the risk of transplant rejection. It is recommended that concomitant use of strong CYP3A4 inducers (such as rifampicin, rifabutin and anti-epileptic medicine such as phenytoin, carbamazepine), with [PRODUCT NAME] should be avoided. If unavoidable, tacrolimus blood

levels should be monitored frequently, starting within the first few days of coadministration, under the supervision of a transplant specialist, to adjust the [PRODUCT NAME] dose if appropriate, in order to maintain similar tacrolimus exposure. Graft function should also be closely monitored (see section 4.5).

Similarly, discontinuation of CYP3A4 inducers may affect the rate of metabolism of [PRODUCT NAME], thereby leading to subtherapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

P-glycoprotein

Caution should be observed when co-administering tacrolimus with medicines that inhibit P-glycoprotein, as an increase in tacrolimus levels may occur. Tacrolimus whole blood levels and the clinical condition of the patient should be monitored closely. An adjustment of the [PRODUCT NAME] dose may be required (see section 4.5).

Herbal preparations

Herbal preparations containing St. John's Wort (Hypericum perforatum) or other herbal preparations should be avoided when taking tacrolimus [PRODUCT NAME] due to the risk of interactions that lead to 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).

Other interactions

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 section 4.2 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).

Vaccination

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.

Nephrotoxicity

[PRODUCT NAME] can result in renal function impairment in post-transplant patients. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. The risk for nephrotoxicity may increase when tacrolimus is concomitantly administered with drugs associated with nephrotoxicity (see section 4.5). Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, tacrolimus trough blood level and renal function should be monitored closely and dosage reduction should be considered if nephrotoxicity occurs.

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, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children 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, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g., initially at three months and then at 9 to 12 months). If abnormalities develop, dose reduction of tacrolimus therapy, 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 [PRODUCT NAME] have been reported to develop Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders (see section 4.8). Patients switched to tacrolimus therapy should not receive anti-lymphocyte treatment concomitantly. Very young (< 2 years), EBV-VCA-negative children 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 [PRODUCT NAME]. 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.

As with other immunosuppressive agents, 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.

As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

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 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.

Infections including opportunistic infections

Patients treated with immunosuppressants, including [PRODUCT NAME] are at increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal) such as BK virus associated nephropathy and 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 physicians 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 [PRODUCT NAME] treatment.

Pure Red Cell Aplasia

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

Special populations

Dose reduction may be necessary in patients with severe liver impairment (see section 4.2).

Excipients:

[PRODUCT NAME] contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take [PRODUCT NAME].

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

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

Metabolic interactions:

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

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. Similarly, discontinuation of such substances may affect the rate of metabolism of [PRODUCT NAME] and thereby the blood levels of tacrolimus. Pharmacokinetic studies have indicated that the increase in tacrolimus blood levels when co-administered with inhibitors of CYP3A4 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.

It is strongly recommended to closely monitor tacrolimus blood levels under supervision of a transplant specialist, as well as monitor for graft function, QT prolongation (with ECG), renal function and other side effects including neurotoxicity, whenever medicines which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly and to interrupt or adjust the [PRODUCT NAME] dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

Similarly, patients should be closely monitored when using [PRODUCT NAME] concomitantly with multiple substances that affect CYP3A4 as the effects on tacrolimus exposure may be enhanced or counteracted.

Medicines which have effects on tacrolimus are listed in the table below. The examples of drug-drug interactions are not intended to be inclusive or comprehensive and therefore the label of each medicine that is co-administered with [PRODUCT NAME] should be consulted for

information related to the route of metabolism, interaction pathways, potential risks and specific actions to be taken with regards to co-administration.

Medicines which have effects on [PRODUCT NAME]

Medicine/Substance Class or Name	**Drug interaction effect**	**Recommendations concerning co-administration**
Grapefruit or grapefruit juice	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see section 4.4].	Avoid grapefruit or grapefruit juice.
High potassium intake, potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone)	May increase tacrolimus associated hyperkalaemia or may increase pre-existing hyperkalaemia.	High potassium intake, or potassium- sparing diuretics should be avoided [see section 4.4].
Ciclosporin	May increase tacrolimus whole blood trough concentrations. In addition, synergistic /additive	The simultaneous use of ciclosporin and tacrolimus should be avoided [see section 4.4].

	nephrotoxic effects can occur.	
Products known to have nephrotoxic or neurotoxic effects: aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, NSAIDs, ganciclovir, acyclovir, amphotericin B, ibuprofen, cidofovir, foscarnet	May enhance nephrotoxic or neurotoxic effects of tacrolimus.	Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, monitor renal function and other side effects and adjust tacrolimus dose if needed.
Strong CYP3A4 inhibitors: antifungal agents (e.g., ketoconazole, itraconazole, posaconazole, voriconazole), the macrolide antibiotics (e.g., telithromycin, troleandomycin, clarithromycin, josamycin), HIV protease inhibitors (e.g., ritonavir, nelfinavir, saquinavir), HCV protease	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., nephrotoxicity, neurotoxicity, QT prolongation) which requires close monitoring [see section 4.4]. Rapid and sharp increases in tacrolimus levels, may occur,	It is recommended that concomitant use should be avoided. If co- administration of a strong CYP3A4 inhibitor is unavoidable, consider omitting the dose of tacrolimus the day the strong CYP3A4 inhibitor is initiated. Reinitiate tacrolimus the next day at a reduced dose based on tacrolimus blood

Initials: DocuSigned by: NM
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 17-Jan-2023 | 12:29:14 GMT
D22075D453FC4A80B696E2507679FFC4

Signature: DocuSigned by: Nkosinathi Mbokane
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 17-Jan-2023 | 12:29:25 GMT
D22075D453FC4A80B696E2507679FFC4

inhibitors (e.g. telaprevir, boceprevir, and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir), nefazodone, the pharmacokinetic enhancer cobicistat, and the kinase inhibitors idelalisib, ceritinib. Strong interactions have also been observed with the macrolide antibiotic erythromycin.	as early as within 1-3 days after co- administration, despite immediate reduction of tacrolimus dose. Overall tacrolimus exposure may increase >5 fold. When ritonavir combinations are co-administered, tacrolimus exposure may increase >50 fold. Nearly all patients may require a reduction in tacrolimus dose and temporary interruption of tacrolimus may also be necessary. The effect on tacrolimus blood concentrations may remain for several days after co-administration is completed.	concentrations. Changes in both tacrolimus dose and/or dosing frequency should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inhibitor. Upon completion, appropriate dose and dosing frequency of tacrolimus should be guided by tacrolimus blood concentrations. Monitor renal function, ECG for QT prolongation, and other side effects closely.

Moderate or weak CYP3A4 inhibitors: antifungal agents (e.g., fluconazole, isavuconazole, clotrimazole, miconazole), the macrolide antibiotics (e.g., azithromycin), calcium channel blockers (e.g., nifedipine, nicardipine, diltiazem, verapamil), amiodarone, danazol, ethinylestradiol, lansoprazole, omeprazole, the HGV antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, the CMV antiviral letermovir, and the tyrosine kinase inhibitors nilotinib, crizotinib, imatinib and (Chinese) herbal remedies containing extracts of *Schisandra sphenanthera*	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see section 4.4]. A rapid increase in tacrolimus level may occur.	Monitor tacrolimus whole blood trough concentrations frequently, starting within the first few days of co-administration. Reduce tacrolimus dose if needed [see section 4.2]. Monitor renal function, ECG for QT prolongation, and other side effects closely.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see section 4.4].	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed [see section 4.2]. Monitor renal function, ECG for QT prolongation, and other side effects closely.
Strong CYP3A4 inducers: rifampicin, phenytoin carbamazepine, apalutamide, enzalutamide, mitotane, or St. John's Wort *(Hypericum perforatum)*	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see section 4.4]. Maximal effect on tacrolimus blood concentrations may be achieved 1-2 weeks after coadministration. The effect may remain 1-2 weeks after completion of the treatment.	It is recommended that concomitant use should be avoided. If unavoidable, patients may require an increase in tacrolimus dose. Changes in tacrolimus dose should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently

		throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inducer. After use of the CYP3A4 inducer has ended, tacrolimus dose may need to be adjusted gradually. Monitor graft function closely.
Moderate CYP3A4 inducers: metamizole, phenobarbital, isoniazid, rifabutin, efavirenz, etravirine, nevirapine	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see section 4.4].	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed [see section 4.2]. Monitor graft function closely.
Cannabidiol (P-gp inhibitor)	There have been reports of increased tacrolimus blood levels during concomitant use of tacrolimus with cannabidiol. This may be due to inhibition of intestinal P-glycoprotein, leading to	Tacrolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor tacrolimus whole blood trough concentrations and adjust the tacrolimus

	increased bioavailability of tacrolimus.	dose if needed [see sections 4.2 and 4.4].
Products known to have high affinity for plasma proteins, e.g.: NSAIDs, oral anticoagulants, oral antidiabetics	Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed [see section 4.2].
Prokinetic agents: metoclopramide, cimetidine and magnesium- aluminium-hydroxide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation).	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed [see section 4.2]. Monitor closely for renal function, for QT prolongation with ECG, and for other side effects.
Maintenance doses of corticosteroids	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see section 4.4].	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed [see section 4.2]. Monitor graft function closely.

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

High dose prednisolone or methylprednisolone	May have impact on tacrolimus blood levels (increase or decrease) when administered for the treatment of acute rejection.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed.
Direct-acting antiviral (DAA) therapy	May have impact on the pharmacokinetics of tacrolimus by changes in liver function during DM therapy, related to clearance of hepatitis virus. A decrease in tacrolimus blood levels may occur. However, the CYP3A4 inhibiting potential of some DMs may counteract that effect or lead to increased tacrolimus blood levels.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed to ensure continued efficacy and safety.

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 not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.4).

Tacrolimus has been shown to 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. Available data suggests that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.

Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine such as phenazone.

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 drug monitoring of mycophenolic acid may be appropriate when switching from ciclosporin to tacrolimus or vice versa.

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 4.4).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

[PRODUCT NAME] is contraindicated in pregnancy. In animal studies (rats and rabbits), [PRODUCT NAME] has been shown to be teratogenic at doses that also demonstrated maternal toxicity. Preclinical and human data show that [PRODUCT NAME] is able to cross the placenta. The possibility of pregnancy should therefore be excluded before initiating [PRODUCT NAME] therapy.

Breastfeeding:

Human data on effects of [PRODUCT NAME] during the lactation period are limited. It has been demonstrated that tacrolimus is excreted into breast milk in animals. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving tacrolimus.

Fertility:

A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats (see section 5.3).

4.7. Effects on ability to drive and use machines:

[PRODUCT NAME] is associated with visual and neurological disturbances. Patients treated with [PRODUCT NAME] who are affected by such disorders should not drive a car or operate dangerous machines. This effect may be enhanced if tacrolimus is given together with alcohol.

4.8. Undesirable effects

Infections and infestations:

Patients receiving [PRODUCT NAME] are frequently at increased risk for infections (viral, bacterial, mycobacterial, fungal, protozoal). Th course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Cases of BK virus (a member of the Polyomavirus family) associated nephropathy, as well as cases of John Cunningham (JC) virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including [PRODUCT NAME].

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Patients receiving immunosuppressive therapy are at increased risk of developing malignancies.

Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with [PRODUCT NAME] treatment.

Blood and lymphatic system disorders:

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

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

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

Immune system disorders:

Allergic and anaphylactoid reactions have been observed in patients receiving [PRODUCT NAME] (see section 4.4).

Endocrine disorders:

Less frequent: hirsutism

Metabolism and nutrition disorders:

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

Less frequent: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Psychiatric disorders:

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

Less frequent: psychotic disorder.

Nervous system disorders:

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

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

Eye disorders:

Frequent: blurred vision, photophobia, eye disorders.

Less frequent: cataract, blindness.

Frequency unknown: optic neuropathy.

Ear and labyrinth disorders:

Frequent: tinnitus.

Less frequent: hypoacusis, neurosensory deafness, impaired hearing.

Cardiac disorders:

Frequent: ischaemic coronary artery disorders, tachycardia.

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

Vascular disorders:

Frequent: hypertension, haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders.

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

Respiratory, thoracic and mediastinal disorders:

Frequent: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations, respiratory failures, respiratory tract disorders, asthma.

Less frequent: acute respiratory distress syndrome.

Gastrointestinal disorders:

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

Less frequent: paralytic ileus, peritonitis, acute and chronic pancreatitis, increased blood amylase, gastroesophageal reflux disease, impaired gastric emptying, subileus, pancreatic pseudocyst.

Hepato-biliary disorders:

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

Less frequent: hepatic artery thrombosis, veno-occlusive liver disease, hepatic failure, bile duct stenosis.

Skin and subcutaneous tissue disorders:

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

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

Musculoskeletal and connective tissue disorders:

Frequent: arthralgia, muscle spasms, pain in limb, back pain.

Less frequent: joint disorders, mobility decreased.

Renal and urinary disorders:

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

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

Reproductive system and breast disorders:

Less frequent: dysmenorrhoea and uterine bleeding.

General disorders and administration site conditions:

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

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

Frequency unknown: febrile neutropenia.

Investigations:

Frequent: hepatic enzymes and function abnormalities, blood alkaline phosphatase increased, weight increased.

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

Injury, poisoning and procedural complications:

Frequent: primary graft dysfunction.

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

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 medicines 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 patientsafety.sacg@novartis.com

4.9. Overdose:

Experience with overdose is limited. Several cases of accidental overdose have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy, renal, neurological and cardiac disturbances, glucose intolerance, hypertension, electrolyte disorders (e.g., hyperkalaemia), increases blood urea nitrogen, and elevated serum creatinine concentrations, and increase in alanine aminotransferase levels.

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

No specific antidote to [PRODUCT NAME] therapy is available. If overdose occurs, general supportive measures and symptomatic treatment should be conducted.

Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma protein binding, it is anticipated that [PRODUCT NAME] will not be dialysable.

In isolated patients with very high plasma levels, hemofiltration or diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcineurin inhibitors

ATC code: L04AD02

Tacrolimus is an immunosuppressive agent with activity in both *in vitro* and *in vivo* experiments. 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.

On 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.

5.2. Pharmacokinetic properties

Absorption:

In the rat, the major site of absorption was identified as the upper gastrointestinal tract.

Absorption of tacrolimus is incomplete and highly variable following oral administration. After oral administration, tacrolimus is variably absorbed. Some patients achieve peak plasma concentrations within 0,5 hours to 3 hours, while in other patients it appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile.

The poor dissolution of tacrolimus in gastric fluids resulting from low aqueous solubility and alterations in gastric motility may be partially responsible for this observation.

In kidney allograft patients, single oral doses of 0,10; 0,15 and 0,2 mg/kg resulted in peak blood concentrations of 19,2; 24,2; and 47,9 ng/ml, respectively. The times to reach peak concentration varied from 0,7 to 6 hours.

The mean bioavailability of tacrolimus capsules was estimated to be 21,8 % in liver transplant patients, 20,1 % in kidney transplant patients, 14,4 to 17,4 % in healthy subjects and 25 % in paediatric liver transplant patients.

In heart allograft recipients tacrolimus is absorbed with a mean time to peak concentration (t_{max}) of approximately 1,5 hours. The oral bioavailability of tacrolimus averages 20 %, however there is a high degree of patient variability in heart transplant patients.

The oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat content. There was a decrease in AUC (plasma 27 %, whole blood 35 %), C_{max} (plasma 50 %, whole blood 57 %), and an increase in t_{max} (both plasma and whole blood 173 %). Both rate and extent of absorption were reduced when tacrolimus was given with food.

Bile does not influence the absorption of tacrolimus, and therefore commencement of tacrolimus therapy with an oral dose and early conversion of liver transplant patients to oral therapy is possible.

Distribution and elimination:

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 α-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.

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. Paediatric liver transplant recipients have a TBC approximately twice that of adult liver transplant patients. 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. In adult and paediatric liver transplant patients, it averaged 11,7 hours and 12,4 hours, respectively, compared with 15,6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

Metabolism and biotransformation:

Tacrolimus is metabolised in the liver, primarily by the cytochrome P450-3A4 family. 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. Only one of the inactive metabolites is present at low concentrations in the systemic circulation. Therefore, metabolites do not meaningfully contribute to the pharmacological activity of tacrolimus.

Excretion:

Following intravenous and oral administration of 14C-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.

Characteristics in patients:

Relationship between plasma/blood concentrations and therapeutic activity:

Individual dose adjustment controlled by monitoring of tacrolimus levels in whole blood may be helpful to achieve optimal therapy. Several immunoassays are available for determining tacrolimus concentrations in whole blood, including a fully automatic micro particle enzyme immunoassay (MEIA).

Variations with respect to confounding factors, age, polymorphism, metabolism and concomitant pathological situations (renal failure, hepatic insufficiency):

Based on limited clinical experience, the kinetic properties of tacrolimus are not altered in elderly patients.

Children require a higher dose of tacrolimus, approximately 1½ to 2 times higher than that recommended for adults, possibly owing to a higher metabolic turnover.

Patients with liver dysfunction:

Patients with liver dysfunction tended to have higher tacrolimus concentrations (and correspondingly longer half-lives and smaller clearance values) compared with patients with normal liver function.

As tacrolimus is extensively metabolised by the liver, patients with impaired liver function should be carefully monitored, and dose adjustment may be necessary (see section 4.2).

Patients with kidney dysfunction:

Since tacrolimus is nearly completely metabolised, highly lipid-soluble, and has a molecular weight of 822 g/mole, it is not expected to be dialysable. Also, less than 1 % of an administered intravenous dose is excreted in the urine. Therefore, changes to the dosing regimen from the pharmacokinetic point of view are not necessary in patients with renal failure or in patients undergoing dialysis. However, dosage adjustment may be necessary in patients with evidence of medicine-induced impairment of kidney function.

5.3 Preclinical safety data

The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus.

When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0,1 to 1,0 mg/kg, QT prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 ng/ml, which is more than 6-fold higher than mean peak concentrations observed with tacrolimus in clinical transplantation.

Embryofoetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic dosages and the offspring showed reduced birth weights, viability and growth. A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Capsule contents:

Hypromellose (Methocel E6 LV)

Lactose monohydrate

Croscarmellose Sodium (Ac Di Sol)

Magnesium stearate

Hard gelatine capsule shell:

[PRODUCT NAME] 0,5 mg:

Gelatine

Titanium dioxide (E 171)

Sodium Lauryl Sulfate

Sorbitan Monolaurate

Yellow iron oxide (E 172)

[PRODUCT NAME] 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)

[PRODUCT NAME] 5 mg:

Gelatine

Titanium dioxide (E 171)

Sodium Lauryl Sulfate

Sorbitan Monolaurate

Red iron oxide (E 172)

6.2. Incompatibilities

Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer a suspension of Tacrolimus capsule contents should not contain PVC.

6.3. Shelf life

24 months

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

After opening the bag, in-use blister pack: 12 months. Store at or below 25 °C.

6.4. Special precautions for storage

Store at or below 30 °C. Store in the original package.

6.5. Nature and contents of container

The primary packaging for [PRODUCT NAME] blisters:

- PVC/ PE Lamite 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.

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

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

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	GRAFTAC 0,5 / GRAFTAC 1 / GRAFTAC 5 TACROLIMUS SANDOZ 0,5 / TACROLIMUS SANDOZ 1 / TACROLIMUS SANDOZ 5
Dosage form and strength	:	Hard gelatin capsules. Each capsule contains tacrolimus monohydrate equal to 0,5 mg, 1 mg and 5 mg, respectively.
Date of submission	:	October 2022

V2.0 (11/10/2022)

Jukskei View

2090

8. REGISTRATION NUMBERS

GRAFTAC 0,5: 43/34/1051

GRAFTAC 1 : 43/34/1052

GRAFTAC 5 : 43/34/1053

TACROLIMUS SANDOZ 0,5 : 43/34/1048

TACROLIMUS SANDOZ 1 : 43/34/1049

TACROLIMUS SANDOZ 5 : 43/34/1050

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 April 2022

10. DATE OF REVISION OF THE TEXT

To be allocated.

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