PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S4**

1. NAME OF THE MEDICINE:

TACROLIMUS 0,5 TEVA

TACROLIMUS 1 TEVA

TACROLIMUS 5 TEVA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

TACROLIMUS 0,5 TEVA: Each capsule contains 0,5 mg tacrolimus.

TACROLIMUS 1 TEVA: Each capsule contains 1,0 mg tacrolimus.

TACROLIMUS 5 TEVA: Each capsule contains 5,0 mg tacrolimus.

Contains Sugar:

Each TACROLIMUS 0,5 TEVA capsule contains 109,1 mg lactose anhydrous.

Each TACROLIMUS 1 TEVA capsule contains 108.6 mg lactose anhydrous.

Each TACROLIMUS 5 TEVA capsule contains 104.6 mg lactose anhydrous.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

TACROLIMUS 0,5 TEVA: Ivory cap and ivory body hard shell capsules with white powder.

TACROLIMUS 1 TEVA: White cap and white body hard shell capsules with white powder.

TACROLIMUS 5 TEVA: Red cap and red body hard shell capsules with white powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

4.2 Posology and method of administration:

General statement:

Tacrolimus therapy requires careful monitoring by adequately qualified and equipped personnel. It should only be prescribed, and changes in immunosuppressive therapy should be initiated by medical practitioners experienced in immunosuppressive therapy and the management of transplant patients.

The dosage recommendations given below for oral administration are intended to act as a guideline. TACROLIMUS TEVA doses should be adjusted according to individual patient requirements.

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

TACROLIMUS TEVA is normally administered together with other immunosuppressive medicines. In isolated cases, successful maintenance therapy with TACROLIMUS TEVA alone has also been described. TACROLIMUS TEVA 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) – general considerations:

Continuous immunosuppression with TACROLIMUS TEVA 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 amount of corticosteroids, introduction of short courses of monoclonal antibodies and increase in the dose of TACROLIMUS TEVA have all been used to manage rejection episodes.

If signs of toxicity are noted, the dose of TACROLIMUS TEVA should be reduced. Patients should be instructed not to decrease the dose without the consent of the treating medical practitioner.

During the course of the post-transplant improvement of the patient, it is likely that the pharmacokinetics of TACROLIMUS TEVA may be altered, requiring adjustment of the TACROLIMUS TEVA dose.

Whole blood concentration monitoring:

Various assays have been used to measure blood or plasma levels of TACROLIMUS TEVA. 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. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Two methods have been used for the assay of tacrolimus, a micro particle enzyme immunoassay (MEIA) and an enzyme linked immunosorbent assay (ELISA). Both methods have been used for the assays must be made with detailed knowledge of the assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetra acetic acid (EDTA) anticoagulant. Heparin anticoagulant is not recommended because of the tendency to form clots during 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.

TACROLIMUS TEVA 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 necessary to measure blood levels on a daily basis. Blood concentration monitoring 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 medicine-medicine interactions.

Clinical experience suggests that the majority of patients can be successfully managed if the blood concentrations of TACROLIMUS TEVA 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.

Primary immunosuppression – Adult patients:

Liver transplantation

Oral administration:

Initially, an oral dose of TACROLIMUS TEVA in a range from 0,10 to 0,20 mg/kg/day should be administered is two divided doses. Initial oral doses have been administered in a range from 0,02 to 0,03 mg/kg/day.

Kidney transplantation

Initial administration:

Initially, an oral dose of TACROLIMUS TEVA in a range from 0,15 to 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, initial intravenous administration should commence 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, initial intravenous administration should commence as a continuous 24 hour infusion.

Maintenance therapy with TACROLIMUS TEVA in liver or kidney transplant recipients:

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

Rescue therapy with TACROLIMUS TEVA:

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

Conversion from ciclosporin to TACROLIMUS TEVA:

The combined administration of ciclosporin and TACROLIMUS TEVA is contraindicated (see **section 4.3**) as TACROLIMUS TEVA 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 TACROLIMUS TEVA based therapy. It is recommended that ciclosporin blood levels are monitored prior to the administration of TACROLIMUS TEVA. The most appropriate time to initiate TACROLIMUS TEVA 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. 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 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, intravenous administration should commence as a continuous 24 hour infusion.

Special populations:

Hepatic impairment:

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

Renal 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 output, is recommended.

Race:

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

Elderly population:

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

Paediatric population:

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

Mode of administration:

Oral 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 **sections 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 blister must be used within 12 months. Patients should be cautioned not to swallow the desiccant contained within the aluminium wrapper.

Duration and onset of oral administration:

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 to any of the excipients listed in **section 6.1** and other macrolides.

Pregnancy and lactation (see **section 4.6**). As TACROLIMUS TEVA 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 inter-changeable with immediate-release formulations of tacrolimus without careful monitoring and supervision by a transplant specialist.

TACROLIMUS TEVA is not recommended for use in children below 18 years due to limited data on safety and/or efficacy.

Tuberculosis must be excluded prior to TACROLIMUS TEVA treatment.

TACROLIMUS TEVA therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources.

TACROLIMUS TEVA 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.

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 over-exposure to TACROLIMUS TEVA. Patients should be maintained on a single formulation of TACROLIMUS TEVA 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 TEVA 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).**

CYP3A4 inhibitors:

Concomitant use with CYP3A4 inhibitors may increase tacrolimus blood levels, which could lead to serious adverse reactions, including nephrotoxicity, neurotoxicity and QT-prolongation. It is recommended that concomitant use of strong CYP3A4 inhibitors (such as ritonavir, cobicistat, ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin or josamycin) with TACROLIMUS TEVA should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of co-administration, under the supervision of a transplant specialist, to adjust the TACROLIMUS TEVA 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 tacrolimus, 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, phenytoin, carbamazepine), with TACROLIMUS TEVA should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of co-administration, under the supervision of a transplant specialist, to adjust the TACROLIMUS TEVA 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 tacrolimus, thereby leading to supratherapeutic 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 TEVA 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 TACROLIMUS TEVA 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 TEVA due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of TACROLIMUS TEVA, or an increase in blood concentrations of tacrolimus and risk of TACROLIMUS TEVA toxicity (see **section 4.5**).

Other interactions:

The combined administration of ciclosporin and TACROLIMUS TEVA is contra-indicated and care should be taken when administering TACROLIMUS TEVA to patients who have previously received ciclosporin (see **sections 4.2** and **4.5**).

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

Certain combinations of TACROLIMUS TEVA with medicines known to have 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:

TACROLIMUS TEVA can result in renal function impairment in post-transplant patients. Acute renal impairment without active intervention may progress to chronic renal impairment. Patients with impaired renal function should be monitored closely as the dosage of TACROLIMUS TEVA may need to be reduced. The risk for nephrotoxicity may increase when TACROLIMUS TEVA is concomitantly administered with medicines associated with nephrotoxicity (see **section 4.5**). Concurrent use of TACROLIMUS TEVA with medicines 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.

Nephrological adverse events can occur throughout the entire treatment period and, in the case of kidney transplant recipients, should be distinguished from symptoms of kidney graft rejection.

Gastrointestinal disorders:

Gastrointestinal perforation has been reported in patients treated with TACROLIMUS TEVA. 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 TEVA in blood may significantly change during diarrhoea episodes, extra monitoring of TACROLIMUS TEVA concentrations is recommended during episodes of diarrhoea.

Cardiac disorders:

Ventricular hypertrophy or hypertrophy of the interventricular septum, reported as cardiomyopathies, has been observed. Most cases have been reversible, occurring primarily in children with TACROLIMUS TEVA 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 TEVA therapy, or change of treatment to another immunosuppressive agent should be considered. TACROLIMUS TEVA 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, bradyarrhythmias 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 TEVA have been reported to develop Epstein-Barr virus (EBV) associated lymphoproliferative disorders (see **section 4.8**). Patients switched to TACROLIMUS TEVA 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 TACROLIMUS TEVA. 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 TEVA have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking TACROLIMUS TEVA 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 TEVA 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 TEVA. 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 TACROLIMUS TEVA are at increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal) such as CMV infection, 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, including graft rejection 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.

Pure Red Cell Aplasia:

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

Excipients:

As TACROLIMUS TEVA contains lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TACROLIMUS TEVA.

The printing ink used to mark TACROLIMUS TEVA capsules 0,5 mg and 1 mg 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 TACROLIMUS TEVA.

4.5 Interaction with other medicines and other forms of interaction:

Metabolic interactions:

Systemically available TACROLIMUS TEVA is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of medicines or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. Similarly, discontinuation of such products or herbal remedies may affect the rate of metabolism of tacrolimus and thereby the blood levels of tacrolimus.

Pharmacokinetics 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 recommended strongly to closely monitor TACROLIMUS TEVA 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 substances which have the potential to alter CYP3A4 metabolism are used concomitantly and to adjust or interrupt the TACROLIMUS TEVA dose if appropriate in order to maintain similar TACROLIMUS TEVA exposure (see **sections 4.2** and **4.4).**

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

Medicines which have effects on tacrolimus, as contained in TACROLIMUS TEVA 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 TACROLIMUS TEVA 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 tacrolimus

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.
Ciclosporin	May increase tacrolimus whole blood trough concentrations. In addition, synergistic/additive nephrotoxic effects can occur.	The simultaneous use of ciclosporin and tacrolimus should be avoided (see **section 4.4**).
Products known to have nephrotoxic or neurotoxic effects:	May enhance nephrotoxic or neurotoxic effects of tacrolimus.	Concurrent use of tacrolimus with medicines known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided,

aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole + trimethoprim, NSAIDs, ganciclovir, acyclovir, amphotericin B, ibuprofen, cidofovir, foscarnet		monitor renal function and other side effects and adjust tacrolimus dose if needed.
Strong CYP3A4 inhibitors: antifungal medicines (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 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	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, as early as within 1 to 3 days after coadministration, 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	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 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,

the kinase inhibitors idelalisib, ceritinib. Strong interactions have also been observed with the macrolide antibiotic erythromycin.	temporary interruption of tacrolimus may also be necessary. The effect on tacrolimus blood concentrations may remain for several days after co-administration is completed.	ECG for QT-prolongation, and other side effects closely.
Moderate or weak CYP3A4 inhibitors: antifungal medicines (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 HCV antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, the CMV antiviral letermovir, and the tyrosine kinase inhibitors nilotinib, crizotinib and imatinib and (Chinese)	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.

herbal remedies containing extracts of *Schisandra sphenanthera*		
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 to 2 weeks after coadministration. The effect may remain 1 to 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; weak CYP3A4 inducers: flucloxacillin	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 increased bioavailability of tacrolimus.	Tacrolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor tacrolimus whole blood trough concentrations and adjust the 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 medicines: metoclopramide, cimetidine and magnesium-aluminium-hydroxide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed (see **section 4.2**). Monitor closely for renal function, for

	reactions (e.g., neurotoxicity, QT-prolongation).	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.
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 DAA therapy, related to clearance of hepatitis virus. A decrease in tacrolimus blood levels may occur. However, the CYP3A4 inhibiting potential of some DAAs 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.

As TACROLIMUS TEVA 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**). Care should be taken when TACROLIMUS TEVA is co-administered with other medicines that increase serum potassium, such as trimethoprim and

cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Close monitoring of serum potassium is recommended.

Effect of tacrolimus on the metabolism of other medicines:

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

The half life of ciclosporin is prolonged when TACROLIMUS TEVA is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and TACROLIMUS TEVA is not recommended and care should be taken when administering TACROLIMUS TEVA to patients who have previously received ciclosporin (see **sections 4.2** and **4.4**).

TACROLIMUS TEVA has been shown to increase the blood level of phenytoin.

As TACROLIMUS TEVA 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 TEVA and statins is available. Available data suggests that the pharmacokinetics of statins is largely unaltered by the coadministration of TACROLIMUS TEVA.

Data have shown that TACROLIMUS TEVA could potentially decrease the clearance and increase the half life of pentobarbital and phenazone.

Mycophenolic acid:

Caution should be exercised when switching combination therapy from ciclosporin, which interferes with enterohepatic recirculation of mycophenolic acid, to TACROLIMUS TEVA, 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 TEVA or vice versa.

Immunosuppressants may affect the response to vaccination and vaccination during treatment with TACROLIMUS TEVA may be less effective. The use of live attenuated vaccines should be avoided (see **section 4.4**).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

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

Breast feeding:

TACROLIMUS TEVA is excreted into breast milk. As detrimental effects on the new-born cannot be excluded, women should not breast-feed whilst receiving TACROLIMUS TEVA.

Fertility:

A negative effect of TACROLIMUS TEVA 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:

TACROLIMUS TEVA may cause visual and neurological disturbances. Patients treated with TACROLIMUS TEVA who are affected by such disorders should not drive or operate dangerous machines. This effect may be enhanced if TACROLIMUS TEVA is administered in association with alcohol.

4.8 Undesirable effects:

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

Many of the adverse reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse reactions compared with intravenous use.

Infections and infestations

As is well known for other potent immunosuppressive agents, patients receiving TACROLIMUS TEVA are frequently at increased risk for infections (viral, bacterial, fungal, and protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Cases of CMV infection, BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including TACROLIMUS TEVA.

Neoplasms benign, malignant and unspecified (incl. 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 TACROLIMUS TEVA 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, febrile neutropenia.

Immune system disorders:

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (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, appetite decreased, 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, writing impaired, nervous system disorders.

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

Frequency unknown: Posterior reversible encephalopathy syndrome (PRES)

Eye disorders:

Frequent: Vision blurred, photophobia, eye disorders.

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: Ventricular dysrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular dysrhythmias, palpitations, pericardial effusion, Torsades de Pointes.

Vascular disorders:

Frequent: Hypertension, haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders.

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

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations.

Less frequent: Respiratory failures, respiratory tract disorders, asthma, and 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: Ileus paralytic, acute and chronic pancreatitis, gastrooesophageal reflux disease, impaired gastric emptying, subileus, pancreatic pseudocyst.

Hepatobiliary disorders:

Frequent: Cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis.

Less frequent: Hepatic artery thrombosis, venoocclusive liver disease, hepatic failure, bile duct stenosis.

Skin and subcutaneous tissue disorders:

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

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

Musculoskeletal and connective tissue disorders:

Frequent: Arthralgia, muscle spasms, pain in extremity, 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.

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.

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

Description of selected adverse reactions:

Pain in extremity has been described in a number of published case reports as part of Calcineurin Inhibitor Induced Pain Syndrome (CIPS). This typically presents as a bilateral and symmetrical, severe, ascending pain in the lower extremities and may be associated with supra therapeutic levels of TACROLIMUS TEVA. The syndrome may respond to tacrolimus dose reduction. In some cases, it was necessary to switch to alternative immunosuppression.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Reactions Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose:

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 postoperative pharmacokinetic variables. Patients with failing liver grafts or those switched from other immunosuppressive therapy to TACROLIMUS TEVA should be monitored carefully to avoid overdosage.

Experience with overdosage is limited. Several cases of accidental overdosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen and elevated serum creatinine concentrations, and increase in alanine aminotransferase levels.

No specific antidote to TACROLIMUS TEVA therapy is available. If overdosage 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 TACROLIMUS TEVA will not be dialysable. In isolated patients with very high plasma levels, haemofiltration or -diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, 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: Immunosuppressants, calcineurin inhibitors, ATC code: L04AD02

Mechanism of action and pharmacodynamic effects:

At the molecular level, the effects of TACROLIMUS TEVA 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 lymphokine genes.

TACROLIMUS TEVA is a highly potent immunosuppressive agent. In particular, TACROLIMUS TEVA inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection.
TACROLIMUS TEVA 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 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:

Distribution of tacrolimus is extensive. It is highly bound to red blood cells and to plasma proteins. Following intravenous infusion of tacrolimus, peak plasma concentrations are reached at the end of the infusion. Concentration declines rapidly after the end of infusion indicating rapid distribution of the medicine outside the plasma compartment. Once distribution equilibrium is reached, tacrolimus concentrations decline at a slower rate, corresponding to the disposition of the medicine.

The pharmacokinetics of tacrolimus after intravenous infusion to transplant patients may be described by a two-compartment model. In kidney transplant patients, the increase in AUC and C_{max} after single oral dose post-transplant was proportional to the increase in oral dose.

In liver transplant patients, the mean trough level concentrations of tacrolimus remained relatively stable up to 6 months post-transplant.

Based on plasma level data in transplant patients, the apparent volume of distribution averaged 1342 l, suggesting extensive distribution of tacrolimus in the body. In liver transplant patients, the volume of distribution averaged 64,4 l based on whole blood concentrations (0,85 l/kg when normalised to body weight) and 1094,5 l based on the plasma concentrations (150,1 l/h or 2,0 l/h/kg when normalised to body weight).

Measurement of minimum blood or plasma levels, which were correlated with AUC, provided an accurate reflection of total tacrolimus exposure.

Tacrolimus is highly bound to plasma proteins (> 98,8 %) in rat, dog, monkey and man. The whole blood/plasma ratio appears to be approximately 20:1 (volunteer studies). Tacrolimus binds strongly to erythrocytes. This effect is dependent on temperature, lower temperatures resulting in lower plasma concentrations.

After oral administration (0,15 mg/kg twice daily) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in most patients.

The half life of tacrolimus is long and variable, and clearance low.

The average total body clearance amounts to approximately 30 ml/min/g (7 to 103 ml/min/kg).

In liver transplant patients, the total body clearance observed was 4,5 l/h (whole blood concentration) and 150,1 l/h or 2,0 l/h/kg when normalised to body weight (plasma concentrations).

The plasma half life of tacrolimus ranges between 3,5 and 40,5 h in renal transplant patients, other references stating up to 50 h.

In liver transplant patients, the elimination half life based on the whole blood concentration averaged 11,7 h (range 6,1 to 20,9 h) and based on the plasma concentration 6,5 h (range 2,7 to 13,3 h).

The renal clearance is less than 1 ml/min. The metabolites of tacrolimus are primarily excreted via the bile.

The mean clearance after oral intake and volume of distribution averaged 0,21 ± 0,08 l/hr/kg and 2,4 ± 0,8 l/kg while t1/2 averaged 8,7 ± 3,5 hrs in heart transplant patients.

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.

Elimination:

Following oral administration of ^{14}C-labelled TACROLIMUS TEVA, 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 TEVA was detected in the urine and faeces, indicating that TACROLIMUS TEVA 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 preliminary clinical experience, the kinetic properties of tacrolimus are not altered in elderly patients. · Children require a higher dose of tacrolimus, approximately one and a half to two 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.

Patients with kidney dysfunction:

Since tacrolimus is nearly completely metabolised, highly lipid-soluble, and has a molecular weight of 822, it is not expected to be dialyzable. 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Capsule content:

Povidone K-30

Croscarmellose sodium (E468)

Lactose

Magnesium stearate

Capsule shell TACROLIMUS 0,5 TEVA:

Titanium dioxide (E171)

Yellow Iron Oxide (E172)

Gelatine

Capsule shell TACROLIMUS 1 TEVA:

Titanium dioxide (E171)

Gelatine

Capsule shell TACROLIMUS 5 TEVA:

Titanium dioxide (E171)

Red Iron Oxide (E172)

Gelatine

6.2 Incompatibilities:

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

6.3 Shelf life:

2 years.

After opening the aluminium wrapper: 1 year.

6.4 Special precautions for storage:

Store at or below 30 °C.

Keep in the original package (within foil pouch), to protect from moisture and light.

6.5 Nature and contents of container:

TACROLIMUS TEVA capsules are packed into transparent PVC/PVdC-Aluminium blister packs. Each blister strip contains 10 capsules.

The blister strips are then packed with a desiccant in an aluminium foil sachet. The foil sachet(s) are placed within an outer carton.

Pack sizes: 20, 30, 50, 60, 90 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

Based on immunosuppressive effects of tacrolimus, inhalation or direct contact with skin or mucous membranes by the formulations for injection, powder or granule contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and flush the affected eye or eyes.

7. MARKETING AUTHORISATION HOLDER:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. MARKETING AUTHORISATION NUMBER(S):

TACROLIMUS 0,5 TEVA: 48/34/0315

TACROLIMUS 1 TEVA: 48/34/0316

TACROLIMUS 5 TEVA: 48/34/0317

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

25 January 2022

10. DATE OF REVISION OF THE TEXT

9 September 2022