Public Assessment Report

Decentralised Procedure

MILOPROSAN/TAMITECT 0.5 MG HARD CAPSULES
MILOPROSAN/TAMITECT 1 MG HARD CAPSULES
MILOPROSAN/TAMITECT 5 MG HARD CAPSULES

TACROLIMUS

UK/H/4470 & 4643/001-3/DC

UK Licence No: PL 23022/0091-6

PHAROS-PHARMACEUTICAL ORIENTED SERVICES LIMITED
LAY SUMMARY

On 19th January 2012, the UK granted Pharos-Pharmaceutical Oriented Services Limited Marketing Authorisations (licences) for Miloprosan/Tamitect 0.5 mg, 1 mg and 5 mg hard capsules (PL 23022/0091-6; UK/H/4470 & 4643/001-3/DC).

Miloprosan/Tamitect 0.5 mg, 1 mg and 5 mg hard capsules contain the active ingredient, tacrolimus.

Miloprosan/Tamitect is an immunosuppressant. Following an organ transplant (e.g. liver, kidney, heart), the body’s immune system will try to reject the new organ. Miloprosan/Tamitect is used to control the body’s immune response enabling the body to accept the transplanted organ.

Miloprosan/Tamitect is often used in combination with other medicines that also suppress the immune system.

Miloprosan/Tamitect may be given for an ongoing rejection of your transplanted liver, kidney, heart or other organ when any previous treatment has been unable to control this immune response after transplantation.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Miloprosan/Tamitect 0.5 mg, 1 mg and 5 mg hard capsules outweigh the risks and these Marketing Authorisations were granted.
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| 1 Introduction |
| 2 Quality aspects |
| 3 Non-clinical aspects |
| 4 Clinical aspects |
| 5 Overall conclusions |
| Module 6: Steps taken after initial procedure | Not applicable |
# Module 1

| **Product Names** | Miloprosan 0.5 mg hard capsules  
|                  | Miloprosan 1 mg hard capsules  
|                  | Miloprosan 5 mg hard capsules  
|                  | Tamitect 0.5 mg hard capsules  
|                  | Tamitect 1 mg hard capsules  
|                  | Tamitect 5 mg hard capsules  |
| **Type of Application** | Generic application, Article 10.1 |
| **Active Substance** | Tacrolimus |
| **Form** | Hard capsules |
| **Strengths** | 0.5 mg  
|              | 1 mg  
|              | 5 mg |
| **MA Holder** | PharOs-Pharmaceutical Oriented Services Ltd  
|                | 87, Marathonos Ave & Salaminas Str.  
|                | 15351 Pallini Attikis  
|                | Greece |
| **Reference Member State (RMS)** | United Kingdom (UK) |
| **Concerned Member States (CMS)** | UK/H/4470/001-3/DC: Germany (DE), Denmark (DK), Finland (FI), the Netherlands (NL), Portugal (PT), the Slovak Republic (SK) and Sweden (SE)  
|                                    | UK/H/4643/001-3/DC: Austria (AT), Germany (DE) and Poland (PL) |
| **Procedure Numbers** | UK/H/4470/001/DC  
|                          | UK/H/4470/002/DC  
|                          | UK/H/4470/003/DC  
|                          | UK/H/4643/001/DC  
|                          | UK/H/4643/002/DC  
|                          | UK/H/4643/003/DC |
| **End of Procedure** | Day 196: 1st November 2011 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Miloprosan 0.5 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Miloprosan 0.5 mg hard capsule contains 0.5 mg tacrolimus

Excipient(s):
Each Miloprosan 0.5 mg hard capsule contains 109.1 mg lactose anhydrous
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Miloprosan 0.5 mg hard capsule: Ivory cap and ivory body hard shell capsules with white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

4.2 Posology and method of administration
Miloprosan therapy requires careful monitoring by adequately qualified and equipped personnel.
The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated,
by physicians experienced in immunosuppressive therapy and the management of transplanted patients.

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations
of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including
under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to
tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding
daily dosing regimen; alterations in formulation or regimen should only take place under the close
supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative
formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that
systemic exposure to tacrolimus is maintained.

General considerations
The recommended initial dosages presented below are intended to act solely as a guideline. tacrolimus
dosing should primarily be based on clinical assessments of rejection and tolerability in each patient
individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If
clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be
considered.

Tacrolimus can be administered intravenously or orally. In general, dosing may commence orally, if
necessary, by administering the capsule contents suspended in water, via nasogastric tubing.
Tacrolimus is routinely administered in conjunction with other immunosuppressive agents in the initial
post-operative period. The Miloprosan dose may vary depending upon the immunosuppressive regimen
chosen.

Method of administration
It is recommended that the oral daily dose be administered in two divided doses (e.g. morning and
evening). Capsules should be taken immediately following removal from the blister. The capsules
should be swallowed with fluid (preferably water).
Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3
hours after a meal, to achieve maximal absorption (see section 5.2).
Patients should be advised not to swallow the desiccant.
Duration of dosing
To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the duration of oral therapy can be given.

Dosage recommendations – Liver transplantation

Prophylaxis of transplant rejection - adults
Oral tacrolimus therapy should commence at 0.10 - 0.20 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery.
If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 - 0.05 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection - children
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 dosing, an initial intravenous dose of tacrolimus 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus monotherapy.
Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Kidney transplantation

Prophylaxis of transplant rejection – adults
Oral tacrolimus therapy should commence at 0.20 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.
If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.05 - 0.10 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection – children
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 dosing, an initial intravenous dose of tacrolimus 0.075 – 0.100 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus-based dualtherapy. Post-
transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation

Prophylaxis of transplant rejection – adults
Tacrolimus can be used with antibody induction (allowing for delayed start of tacrolimus therapy) or alternatively in clinically stable patients without antibody induction.
Following antibody induction, oral tacrolimus therapy should commence at a dose of 0.075 mg/kg/day administered as two divided doses (e.g. morning and evening).
Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilized. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.
An alternative strategy was published where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection – children
Tacrolimus has been used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if tacrolimus therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 – 25 ng/ml.
Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.
Following antibody induction, if tacrolimus therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening).

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. In adult patients converted to tacrolimus, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g. morning and evening).
In paediatric patients converted to tacrolimus, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in two divided doses (e.g. morning and evening).
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Rejection therapy, other allografts
The dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data. In lung-transplanted patients tacrolimus has been used at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.
Dosage adjustments in special populations

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

Renal impairment
As the pharmacokinetics of tacrolimus are unaffected by renal function (see section 5.2), no dose adjustment is required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender: There is no evidence that male and female patients require different doses to achieve similar trough levels.

Paediatric patients
In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

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

Conversion from cyclosporine
Care should be taken when converting patients from cyclosporine-based to tacrolimus based therapy (see sections 4.4 and 4.5). The combined administration of cyclosporine and tacrolimus is not recommended. Tacrolimus therapy should be initiated after considering cyclosporine blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporine blood levels. In practice, tacrolimus therapy has been initiated 12 - 24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued following conversion as the clearance of cyclosporine might be affected.

Therapeutic drug monitoring
Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring.
As an aid to optimize dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood including a semi-automated microparticle enzyme immunoassay (MEIA). Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods.

Blood trough levels of tacrolimus should be monitored during the post-transplantation period. When dosed orally, blood trough levels should be drawn approximately 12 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As Miloprosan is a medicinal product with low clearance, adjustments to the dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5).

Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

In clinical practice, whole blood trough levels have generally been in the range 5 – 20 ng/ml in liver transplant recipients and 10 – 20 ng/ml in kidney and heart transplant patients in the early post transplant period. Subsequently, during maintenance therapy, blood concentrations have generally been in the range of 5 – 15 ng/ml in liver, kidney and heart transplant recipients.
4.3 **Contraindications**

Hypersensitivity to tacrolimus or other macrolides.

Hypersensitivity to any of the excipients (see section 6.1).

4.4 **Special warnings and precautions for use**

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, hematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

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

Herbal preparations containing St. John’s Wort (Hypericum perforatum) should be avoided when taking Miloprosan due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus (see section 4.5).

The combined administration of cyclosporine and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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.

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 in tacrolimus treated patients 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 9-12 months). If abnormalities develop, dose reduction of tacrolimus, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.
Lymph proliferative disorders and malignancies

Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to tacrolimus therapy should not receive antilymphocyte 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. 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 potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

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.

Patients treated with immunosuppressants, including tacrolimus are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). 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 renal function or neurological symptoms.

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Special populations

There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA).

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

Miloprosan contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Systemically available tacrolimus is metabolized by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels

Clinically the following substances have been shown to increase tacrolimus blood levels: Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (e.g. ritonavir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nifedipine, norethisterone, quinidine, tamoxifen, troleandomycin.

Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided. Lansoprazol and cyclosporine may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

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

Other potential interactions that may increase systemic exposure of tacrolimus include prokinetic agents (such as metoclopramide and cisapride), cinemidine and magnesiumaluminium-hydroxide.

CYP3A4 inducers potentially leading to decreased tacrolimus blood levels
Clinically the following substances have been shown to decrease tacrolimus blood levels: Strong interactions have been observed with rifampicin, phenytoin or St. John’s Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels. Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

Effect of tacrolimus on the metabolism of other medicinal products
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolized by CYP3A4 may affect the metabolism of such medicinal products. The half-life of cyclosporine is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 phenazone.

Other interactions leading to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gryase inhibitors, vancomycin, sulfamethoxazole+trimethoprim, NSAIDs, ganciclovir or aciclovir). Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.

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

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided (see section 4.4).
4.6 Fertility, Pregnancy and lactation

Human data show that tacrolimus cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the fetus. In case of in utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn, (incidence 8 of 111 neonates, i.e. 7.2%), which, however, normalizes spontaneously. In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

Lactation
Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving <PRODUCT NAME>.

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
Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Miloprosan is administered in association with alcohol. No studies on the effects of tacrolimus on the ability to drive and use machines have been performed.

4.8 Undesirable effects
The adverse drug 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 drug reactions stated below are reversible and/or respond to dose reduction. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders
common: ischaemic coronary artery disorders, tachycardia
uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal
rare: pericardial effusion
very rare: echocardiogram abnormal

Blood and lymphatic system disorders
common: anaemia, leukopenia, thrombocytopenia, leukocytosis red blood cell analyses abnormal,
uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia,
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

Nervous system disorders
very common: headache, tremor
common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders

uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia

rare: hypertonia

very rare: myasthenia

Eye disorders
common: vision blurred, photophobia, eye disorders

uncommon: cataract

rare: blindness

Ear and labyrinth disorders
common: tinnitus

uncommon: hypoacusis

rare: deafness neurosensory

very rare: hearing impaired

Respiratory, thoracic and mediastinal disorders
common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis cough, nasal congestion and inflammations

uncommon: respiratory failures, respiratory tract disorders, asthma

rare: acute respiratory distress syndrome

Gastrointestinal disorders
very common: diarrhoea, nausea

common: 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

uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastro oesophageal reflux disease, impaired gastric emptying

rare: subileus, pancreatic pseudocyst

Renal and urinary disorders
very common: renal impairment

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

uncommon: anuria, haemolytic uraemic syndrome

very rare: nephropathy, cystitis haemorrhagic

Skin and subcutaneous tissue disorders
common: pruritus, rash, alopecias, acne, sweating increased
uncommon: dermatitis, photosensitivity

rare: toxic epidermal necrolysis (Lyell’s syndrome)

very rare: Stevens Johnson syndrome

Musculoskeletal and connective tissue disorders
common: arthralgia, muscle cramps, pain in limb, back pain,

uncommon: joint disorders

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia

common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia,
hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia,
metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia,
other electrolyte abnormalities,

uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are
frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of preexisting
infections may be aggravated. Both generalized and localized infections can occur. Cases of BK virus
associated nephropathy, as well as cases of JC virus associated progressive multifocal
leukencephalopathy (PML), have been reported in patients treated with immunosuppressants,
including tacrolimus

Injury, poisoning and procedural complications
common: primary graft dysfunction

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

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 treatment.

Vascular disorders
very common: hypertension

common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders
vascular hypotensive disorders

uncommon: infarction, venous thrombosis deep limb, shock

General disorders and administration site conditions
common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline
phosphatase increased, weight increased, body temperature perception disturbed

uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure
sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased,
weight decreased.
rare: thirst, fall, ulcer, chest tightness, mobility decreased

very rare: fat tissue increased

**Immune system disorders**

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4).

**Hepatobiliary disorders**

common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis

rare: hepatitic artery thrombosis, venoocclusive liver disease

very rare: hepatic failure, bile duct stenosis

**Reproductive system and breast disorders**

uncommon: dysmenorrhoea and uterine bleeding

**Psychiatric disorders**

very common: insomnia

common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders,

uncommon: psychotic disorder

4.9 Overdose

Experience with over dosage is limited. Several cases of accidental over dosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen serum creatinine and increase in alanine aminotransferase levels. No specific antidote to Miloprosan therapy is available. If over dosage 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 will not be dialyzable. In isolated patients with very high plasma levels, haemofiltration 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 inhibitor, ATC code: L04AD02

**Mechanism of action**

At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.

Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both *in vitro* and *in vivo* experiments.

In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.
Clinical efficacy and safety of tacrolimus capsules bid in primary organ transplantation

In prospective published studies tacrolimus was investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of tacrolimus in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus was used as primary treatment in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarized below.

Lung transplantation

The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomization to either tacrolimus or cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus cyclosporine-treated patients (11.5 % versus 22.6 %) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86 % versus 8.57 %), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8 % in the tacrolimus and 83 % in the cyclosporine group.

Another randomized study included 66 patients on tacrolimus versus 67 patients on cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/ml. The 1-year patient survival was 83 % in the tacrolimus and 71 % in the cyclosporine group, the 2-year survival rates were 76 % and 66 %, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the cyclosporine group (1.09 episodes). Obliterative bronchiolitis developed in 21.7 % of patients in the tacrolimus group compared with 38.0 % of patients in the cyclosporine group (p = 0.025). Significantly more cyclosporine-treated patients (n = 13) required a switch to tacrolimus than tacrolimus-treated patients to cyclosporine (n = 2) (p = 0.02) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomized to the tacrolimus versus 24 patients to the cyclosporine group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml.

The 1-year survival rates were 73.1 % in the tacrolimus versus 79.2 % in the cyclosporine group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7 % versus 45.8 %) and at 1 year after lung transplantation (50 % versus 33.3 %).

The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

Pancreas transplantation

A multicentre study included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomized to tacrolimus (n=103) or to cyclosporine (n=102). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6.

Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3 % versus 74.5 % with cyclosporine (p < 0.0005), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from cyclosporine to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy.

Intestinal transplantation

Published clinical experience from a single centre on the use of tacrolimus for primary treatment following intestinal transplantation showed that the actuarial survival rate of 155 patients (65 intestine alone, 75 liver and intestine, and 25 multivisceral) receiving tacrolimus and prednisone was 75 % at 1 year, 54 % at 5 years, and 42 % at 10 years. In the early years the initial oral dose of tacrolimus was 0.3 mg/kg/day. Results continuously improved with increasing experience over the course of 11 years. A variety of innovations, such as techniques for early detection of Epstein-Barr (EBV) and CMV infections, bone marrow augmentation, the adjunct use of the interleukin-2 antagonist daclizumab,
5.2 Pharmacokinetic properties

Absorption

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus capsules peak concentrations (Cmax) of tacrolimus in blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20 % - 25 %.

After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients. In healthy subjects, tacrolimus 0.5 mg, tacrolimus 1 mg and tacrolimus 5 mg capsules, hard have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34 % of calories) content. Decreases in AUC (27 %) and Cmax (50 %), and an increase in tmax (173 %) in whole blood were evident.

In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12 %) and Cmax (15 to 38 %), and an increase in tmax (38 to 80 %) in whole blood were evident.

Bile flow does not influence the absorption of tacrolimus.

A strong correlation exists between AUC and whole blood trough levels at steady-state. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

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.

Metabolism and biotransformation

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

Excretion

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. 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.
Following intravenous and oral administration of 14C-labelled tacrolimus, most of the radioactivity was eliminated in the feces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and feces, indicating that tacrolimus is almost completely metabolized prior to elimination: bile being the principal route of elimination.

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. Embryofetal 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 content:
Povidone K-30
Croscarmellose sodium (E468)
Lactose anhydrous
Magnesium stearate

Miloprosan 0.5 mg Capsule shells:
Titanium dioxide (E171)
Yellow Iron Oxide (E-172)
Gelatin

6.2 Incompatibilities
Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer a suspension of Miloprosan 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 below 30°C, in the original package, to protect from moisture & light.

6.5 Nature and contents of container
PVC/PVdC-Aluminium blister pack
10 capsules per blister. Blisters placed with a desiccant in an aluminium foil sachet.

Pack sizes:
20, 30, 50 and 100 capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORITY ORGANISATION
PharOs-Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Salaminas Str.
15351 Pallini Attikis
Greece

8 MARKETING AUTHORITY NUMBER(S)
PL23022/0091
1 NAME OF THE MEDICINAL PRODUCT
Miloprosan 1 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Miloprosan 1 mg hard capsule contains 1 mg tacrolimus

Excipient(s):
Each Miloprosan 1 mg hard capsule contains 108.6 mg lactose anhydrous
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Miloprosan 1 mg hard capsule: White cap and white body hard shell capsules with white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

4.2 Posology and method of administration
Miloprosan therapy requires careful monitoring by adequately qualified and equipped personnel.
The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated,
by physicians experienced in immunosuppressive therapy and the management of transplanted patients.

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations
of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including
under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to
tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding
daily dosing regimen; alterations in formulation or regimen should only take place under the close
supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative
formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that
systemic exposure to tacrolimus is maintained.

General considerations
The recommended initial dosages presented below are intended to act solely as a guideline. tacrolimus
dosing should primarily be based on clinical assessments of rejection and tolerability in each patient
individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If
clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be
considered.

Tacrolimus can be administered intravenously or orally. In general, dosing may commence orally, if
necessary, by administering the capsule contents suspended in water, via nasogastric tubing.
Tacrolimus is routinely administered in conjunction with other immunosuppressive agents in the initial
post-operative period. The Miloprosan dose may vary depending upon the immunosuppressive regimen
chosen.

Method of administration
It is recommended that the oral daily dose be administered in two divided doses (e.g. morning and
evening). Capsules should be taken immediately following removal from the blister. The capsules
should be swallowed with fluid (preferably water).
Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3
hours after a meal, to achieve maximal absorption (see section 5.2).
Patients should be advised not to swallow the desiccant.

Duration of dosing
To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the
duration of oral therapy can be given.
Dosage recommendations – Liver transplantation

Prophylaxis of transplant rejection - adults
Oral tacrolimus therapy should commence at 0.10 - 0.20 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 - 0.05 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection - children
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 dosing, an initial intravenous dose of tacrolimus 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Kidney transplantation

Prophylaxis of transplant rejection – adults
Oral tacrolimus therapy should commence at 0.20 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.05 - 0.10 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection – children
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 dosing, an initial intravenous dose of tacrolimus 0.075 – 0.100 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus-based dualtherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.
Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation
Prophylaxis of transplant rejection – adults
Tacrolimus can be used with antibody induction (allowing for delayed start of tacrolimus therapy) or alternatively in clinically stable patients without antibody induction.
Following antibody induction, oral tacrolimus therapy should commence at a dose of 0.075 mg/kg/day administered as two divided doses (e.g. morning and evening).
Administration should commence within 5 days after the completion of surgery as soon as the patient’s clinical condition is stabilized. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.
An alternative strategy was published where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection – children
Tacrolimus has been used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if tacrolimus therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 – 25 ng/ml.
Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.
Following antibody induction, if tacrolimus therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening).

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. In adult patients converted to tacrolimus, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g. morning and evening).
In paediatric patients converted to tacrolimus, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in two divided doses (e.g. morning and evening).
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Rejection therapy, other allografts
The dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data. In lung-transplanted patients tacrolimus has been used at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

Dosage adjustments in special populations
Hepatic impairment
Dose reduction may be necessary in patients with severe liver impairment in order to maintain the tacrolimus blood trough levels within the recommended target range.
Renal impairment
As the pharmacokinetics of tacrolimus are unaffected by renal function (see section 5.2), no dose adjustment is required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender: There is no evidence that male and female patients require different doses to achieve similar trough levels.

Paediatric patients
In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

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

Conversion from cyclosporine
Care should be taken when converting patients from cyclosporine-based to tacrolimus based therapy (see sections 4.4 and 4.5). The combined administration of cyclosporine and tacrolimus is not recommended. Tacrolimus therapy should be initiated after considering cyclosporine blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporine blood levels. In practice, tacrolimus therapy has been initiated 12 - 24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued following conversion as the clearance of cyclosporine might be affected.

Therapeutic drug monitoring
Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring. As an aid to optimize dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood including a semi-automated microparticle enzyme immunoassay (MEIA). Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. Blood trough levels of tacrolimus should be monitored during the post-transplantation period. When dosed orally, blood trough levels should be drawn approximately 12 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As Miloprosan is a medicinal product with low clearance, adjustments to the dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5).

Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

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

4.3 Contraindications
Hypersensitivity to tacrolimus or other macrolides.
Hypersensitivity to any of the excipients (see section 6.1).
4.4 Special warnings and precautions for use

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, hematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

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

Herbal preparations containing St. John’s Wort (Hypericum perforatum) should be avoided when taking Miloprosan due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus (see section 4.5).

The combined administration of cyclosporine and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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.

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 in tacrolimus treated patients 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 9-12 months). If abnormalities develop, dose reduction of tacrolimus, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.

Lymph proliferative disorders and malignancies

Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to tacrolimus therapy should not receive antilymphocyte 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. 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 potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

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.

Patients treated with immunosuppressants, including tacrolimus are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). 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 renal function or neurological symptoms.

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Special populations
There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA).

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

Miloprosan contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Systemically available tacrolimus is metabolized by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels
Clinically the following substances have been shown to increase tacrolimus blood levels: Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (e.g. ritonavir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided. Lansoprazol and cyclosporine may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

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

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

CYP3A4 inducers potentially leading to decreased tacrolimus blood levels
Clinically the following substances have been shown to decrease tacrolimus blood levels: Strong interactions have been observed with rifampicin, phenytoin or St. John’s Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients.

CYP3A4 inducers potentially leading to decreased tacrolimus blood levels
Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

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

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

Effect of tacrolimus on the metabolism of other medicinal products
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolized by CYP3A4 may affect the metabolism of such medicinal products.

The half-life of cyclosporine is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 phenzone.

Other interactions leading to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole-trimethoprim, NSAIDs, ganciclovir or aciclovir).

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

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

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

4.6 Fertility, Pregnancy and lactation
Human data show that tacrolimus cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to
the fetus. In case of in utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn, (incidence 8 of 111 neonates, i.e. 7.2%), which, however, normalizes spontaneously. In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

Lactation
Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving <PRODUCT NAME>.

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
Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Miloprosan is administered in association with alcohol. No studies on the effects of tacrolimus on the ability to drive and use machines have been performed.

4.8 Undesirable effects
The adverse drug 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 drug reactions stated below are reversible and/or respond to dose reduction. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders
common: ischaemic coronary artery disorders, tachycardia
uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal
rare: pericardial effusion
very rare: echocardiogram abnormal

Blood and lymphatic system disorders
common: anaemia, leukopenia, thrombocytopenia, leukocytosis red blood cell analyses abnormal,
uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia,
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

Nervous system disorders
very common: headache, tremor
common: seizures, disturbances in consciousness, paraesthesias and dysesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders
uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare: hypertonia
very rare: myasthenia

**Eye disorders**
common: vision blurred, photophobia, eye disorders
uncommon: cataract
rare: blindness

**Ear and labyrinth disorders**
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

**Respiratory, thoracic and mediastinal disorders**
common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis cough, nasal congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome

**Gastrointestinal disorders**
very common: diarrhoea, nausea
common: 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
uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastro oesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

**Renal and urinary disorders**
very common: renal impairment
common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhagic

**Skin and subcutaneous tissue disorders**
common: pruritus, rash, alopecias, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell’s syndrome)
very rare: Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders
common: arthralgia, muscle cramps, pain in limb, back pain,
uncommon: joint disorders

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia,
hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia,
metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia,
other electrolyte abnormalities,
uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of preexisting infections may be aggravated. Both generalized and localized infections can occur. Cases of 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

Injury, poisoning and procedural complications
common: primary graft dysfunction
Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).

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 treatment.

Vascular disorders
very common: hypertension
common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders
vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock

General disorders and administration site conditions
common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed
uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased.
rare: thirst, fall, ulcer, chest tightness, mobility decreased
very rare: fat tissue increased
Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4).

Hepatobiliary disorders
common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
rare: hepatitic artery thrombosis, venoocclusive liver disease
very rare: hepatic failure, bile duct stenosis

Reproductive system and breast disorders
uncommon: dysmenorrhoea and uterine bleeding

Psychiatric disorders
very common: insomnia
common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders,
uncommon: psychotic disorder

4.9 Overdose
Experience with over dosage is limited. Several cases of accidental over dosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen serum creatinine and increase in alanine aminotransferase levels. No specific antidote to Miloprosan therapy is available. If over dosage 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 will not be dialyzable. In isolated patients with very high plasma levels, haemofiltration 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 inhibitor, ATC code: L04AD02

Mechanism of action
At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.
Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both in vitro and in vivo experiments.

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

Clinical efficacy and safety of tacrolimus capsules bid in primary organ transplantation
In prospective published studies tacrolimus was investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of tacrolimus in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus was used as primary treatment
in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarized below.

**Lung transplantation**

The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomization to either tacrolimus or cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus cyclosporine-treated patients (11.5% versus 22.6%) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86% versus 8.57%), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8% in the tacrolimus and 83% in the cyclosporine group.

Another randomized study included 66 patients on tacrolimus versus 67 patients on cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/ml. The 1-year patient survival was 83% in the tacrolimus and 71% in the cyclosporine group, the 2-year survival rates were 76% and 66%, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the cyclosporine group (1.09 episodes). Obliterative bronchiolitis developed in 21.7% of patients in the tacrolimus group compared with 38.0% of patients in the cyclosporine group (p = 0.025). Significantly more cyclosporine-treated patients (n = 13) required a switch to tacrolimus than tacrolimus-treated patients to cyclosporine (n = 2) (p = 0.02) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomized to the tacrolimus versus 24 patients to the cyclosporine group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml.

The 1-year survival rates were 73.1% in the tacrolimus versus 79.2% in the cyclosporine group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7% versus 45.8%) and at 1 year after lung transplantation (50% versus 33.3%).

The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

**Pancreas transplantation**

A multicentre study included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomized to tacrolimus (n=103) or to cyclosporine (n=102). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6.

Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3% versus 74.5% with cyclosporine (p < 0.0005), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from cyclosporine to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy.

**Intestinal transplantation**

Published clinical experience from a single centre on the use of tacrolimus for primary treatment following intestinal transplantation showed that the actuarial survival rate of 155 patients (65 intestine alone, 75 liver and intestine, and 25 multivisceral) receiving tacrolimus and prednisone was 75% at 1 year, 54% at 5 years, and 42% at 10 years. In the early years the initial oral dose of tacrolimus was 0.3 mg/kg/day. Results continuously improved with increasing experience over the course of 11 years. A variety of innovations, such as techniques for early detection of Epstein-Barr (EBV) and CMV infections, bone marrow augmentation, the adjunct use of the interleukin-2 antagonist daclizumab, lower initial tacrolimus doses with target trough levels of 10 to 15 ng/ml, and most recently allograft irradiation were considered to have contributed to improved results in this indication over time.
5.2 Pharmacokinetic properties

Absorption
In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus capsules peak concentrations (Cmax) of tacrolimus in blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20 % - 25 %.

After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients. In healthy subjects, tacrolimus 0.5 mg, tacrolimus 1 mg and tacrolimus 5 mg capsules, hard have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34 % of calories) content. Decreases in AUC (27 %) and Cmax (50 %), and an increase in tmax (173 %) in whole blood were evident. In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12 %) and Cmax (15 to 38 %), and an increase in tmax (38 to 80 %) in whole blood were evident.

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

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.

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

Excretion
Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. 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.

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

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. Embryofetal 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 content:
Povidone K-30
Croscarmellose sodium (E468)
Lactose anhydrous
Magnesium stearate

Miloprosan1 mg Capsule shells:
Titanium dioxide (E171)
Gelatin

6.2 Incomaptibilities
Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer a suspension of Miloprosan 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 below 30°C, in the original package, to protect from moisture & light.

6.5 Nature and contents of container
PVC/PVdC-Aluminium blister pack
10 capsules per blister. Blisters placed with a desiccant in an aluminium foil sachet.
Pack sizes:
20, 50, 60 and 100 capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
PharOs-Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Salaminas Str.
15351 Pallini Attikis
Greece

8 MARKETING AUTHORISATION NUMBER(S)
PL23022/0092

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/01/2012

10 DATE OF REVISION OF THE TEXT
19/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Miloprosan 5 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Miloprosan 5 mg hard capsule contains 5 mg tacrolimus

Excipient(s):
Each Miloprosan 5 mg hard capsule contains 108.6 mg lactose anhydrous
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Miloprosan 1 mg hard capsule: 5 mg hard capsule: Red cap and red body hard shell capsules with white powder

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

4.2 Posology and method of administration
Miloprosan therapy requires careful monitoring by adequately qualified and equipped personnel. The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplanted patients.

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

General considerations
The recommended initial dosages presented below are intended to act solely as a guideline. tacrolimus dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

Tacrolimus can be administered intravenously or orally. In general, dosing may commence orally, if necessary, by administering the capsule contents suspended in water, via nasogastric tubing. Tacrolimus is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The Miloprosan dose may vary depending upon the immunosuppressive regimen chosen.

Method of administration
It is recommended that the oral daily dose be administered in two divided doses (e.g. morning and evening). Capsules should be taken immediately following removal from the blister. The capsules should be swallowed with fluid (preferably water).
Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption (see section 5.2).
Patients should be advised not to swallow the desiccant.

Duration of dosing
To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the duration of oral therapy can be given.
Dosage recommendations – Liver transplantation

Prophylaxis of transplant rejection - adults
Oral tacrolimus therapy should commence at 0.10 - 0.20 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery.
If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 - 0.05 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection - children
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 dosing, an initial intravenous dose of tacrolimus 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Kidney transplantation

Prophylaxis of transplant rejection – adults
Oral tacrolimus therapy should commence at 0.20 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.
If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.05 - 0.10 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection – children
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 dosing, an initial intravenous dose of tacrolimus 0.075 – 0.100 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus-based dualtherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.
Rejection therapy – adults and children

Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.

For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation

Prophylaxis of transplant rejection – adults

Tacrolimus can be used with antibody induction (allowing for delayed start of tacrolimus therapy) or alternatively in clinically stable patients without antibody induction.

Following antibody induction, oral tacrolimus therapy should commence at a dose of 0.075 mg/kg/day administered as two divided doses (e.g. morning and evening).

Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilized. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.

An alternative strategy was published where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection – children

Tacrolimus has been used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if tacrolimus therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 – 25 ng/ml.

Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.

Following antibody induction, if tacrolimus therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening).

Dose adjustment during post-transplant period in adults and children

Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children

Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. In adult patients converted to tacrolimus, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g. morning and evening).

In paediatric patients converted to tacrolimus, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in two divided doses (e.g. morning and evening).

For information on conversion from cyclosporine to Miloprosan, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Rejection therapy, other allografts

The dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data. In lung-transplanted patients tacrolimus has been used at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

Dosage adjustments in special populations

Hepatic impairment

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

As the pharmacokinetics of tacrolimus are unaffected by renal function (see section 5.2), no dose adjustment is required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender: There is no evidence that male and female patients require different doses to achieve similar trough levels.

**Paediatric patients**

In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

**Elderly patients**

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

**Conversion from cyclosporine**

Care should be taken when converting patients from cyclosporine-based to tacrolimus based therapy (see sections 4.4 and 4.5). The combined administration of cyclosporine and tacrolimus is not recommended. Tacrolimus therapy should be initiated after considering cyclosporine blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporine blood levels. In practice, tacrolimus therapy has been initiated 12 - 24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued following conversion as the clearance of cyclosporine might be affected.

**Therapeutic drug monitoring**

Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring. As an aid to optimize dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood including a semi-automated microparticle enzyme immunoassay (MEIA). Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. Blood trough levels of tacrolimus should be monitored during the post-transplantation period. When dosed orally, blood trough levels should be drawn approximately 12 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As Miloprosan is a medicinal product with low clearance, adjustments to the dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5).

Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

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

4.3 **Contraindications**

Hypersensitivity to tacrolimus or other macrolides.
Hypersensitivity to any of the excipients (see section 6.1).
4.4 Special warnings and precautions for use

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, hematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

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

Herbal preparations containing St. John’s Wort (Hypericum perforatum) should be avoided when taking Miloprosan due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus (see section 4.5).

The combined administration of cyclosporine and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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.

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 in tacrolimus treated patients 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 9-12 months). If abnormalities develop, dose reduction of tacrolimus, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.

**Lymph proliferative disorders and malignancies**

Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to tacrolimus therapy should not receive antilymphocyte 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. 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 potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

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.

Patients treated with immunosuppressants, including tacrolimus are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). 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 renal function or neurological symptoms.

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Special populations
There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA).

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

Miloprosan contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Systemically available tacrolimus is metabolized by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels
Clinically the following substances have been shown to increase tacrolimus blood levels: Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (e.g. ritonavir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided. Lansoprazol and cyclosporine may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

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

Other potential interactions that may increase systemic exposure of tacrolimus include prokinetic agents (such as metoclopramide and cisapride), cimetidine and magnesiumaluminium hydroxide.

CYP3A4 inducers potentially leading to decreased tacrolimus blood levels
Clinically the following substances have been shown to decrease tacrolimus blood levels: Strong interactions have been observed with rifampicin, phenytoin or St. John’s Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels. Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

Effect of tacrolimus on the metabolism of other medicinal products
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolized by CYP3A4 may affect the metabolism of such medicinal products. The half-life of cyclosporine is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 phenazone.

Other interactions leading to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole+trimethoprim, NSAIDs, ganciclovir or aciclovir).

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

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

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

4.6 Fertility, Pregnancy and lactation
Human data show that tacrolimus cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to
the fetus. In case of in utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn, (incidence 8 of 111 neonates, i.e. 7.2%), which, however, normalizes spontaneously. In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

Lactation
Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving <PRODUCT NAME>.

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
Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Miloprosan is administered in association with alcohol. No studies on the effects of tacrolimus on the ability to drive and use machines have been performed.

4.8 Undesirable effects
The adverse drug 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 drug reactions stated below are reversible and/or respond to dose reduction. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders
common: ischaemic coronary artery disorders, tachycardia
uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal
rare: pericardial effusion
very rare: echocardiogram abnormal

Blood and lymphatic system disorders
common: anaemia, leukopenia, thrombocytopenia, leukocytosis red blood cell analyses abnormal,
uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia,
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

Nervous system disorders
very common: headache, tremor
common: seizures, disturbances in consciousness, paraesthesias and dysesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders
uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare: hypertonia
very rare: myasthenia

Eye disorders
common: vision blurred, photophobia, eye disorders
uncommon: cataract
rare: blindness

Ear and labyrinth disorders
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

Respiratory, thoracic and mediastinal disorders
common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis cough, nasal congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome

Gastrointestinal disorders
very common: diarrhoea, nausea
common: 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
uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastro oesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

Renal and urinary disorders
very common: renal impairment
common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhagic

Skin and subcutaneous tissue disorders
common: pruritus, rash, alopecias, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell’s syndrome)
very rare: Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders
common: arthralgia, muscle cramps, pain in limb, back pain,
uncommon: joint disorders

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia,
hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia,
metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia,
other electrolyte abnormalities,
uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are
frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of preexisting
infections may be aggravated. Both generalized and localized infections can occur. Cases of BK virus
associated nephropathy, as well as cases of JC virus associated progressive multifocal
leuкоencephalopathy (PML), have been reported in patients treated with immunosuppressants,
including tacrolimus

Injury, poisoning and procedural complications
common: primary graft dysfunction

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

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 treatment.

Vascular disorders
very common: hypertension
common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders
vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock

General disorders and administration site conditions
common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline
phosphatase increased, weight increased, body temperature perception disturbed
uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure
sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased,
weight decreased.
rare: thirst, fall, ulcer, chest tightness, mobility decreased
very rare: fat tissue increased

Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section
4.4).

Hepatobiliary disorders
common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular
damage and hepatitis, cholangitis
rare: hepatitic artery thrombosis, venoocclusive liver disease

very rare: hepatic failure, bile duct stenosis

Reproductive system and breast disorders
uncommon: dysmenorrhoea and uterine bleeding

Psychiatric disorders
very common: insomnia
common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders,
uncommon: psychotic disorder

4.9 Overdose
Experience with overdosage is limited. Several cases of accidental overdosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen serum creatinine and increase in alanine aminotransferase levels. No specific antidote to Miloprosan 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 will not be dialyzable. In isolated patients with very high plasma levels, haemofiltration or -dialfiltration 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 inhibitor, ATC code: L04AD02

Mechanism of action
At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.

Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both in vitro and in vivo experiments.

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

Clinical efficacy and safety of tacrolimus capsules bid in primary organ transplantation
In prospective published studies tacrolimus was investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of tacrolimus in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus was used as primary treatment in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarized below.
Lung transplantation
The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomization to either tacrolimus or cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus-versus cyclosporine-treated patients (11.5 % versus 22.6 %) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86 % versus 8.57 %), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8 % in the tacrolimus and 83 % in the cyclosporine group.

Another randomized study included 66 patients on tacrolimus versus 67 patients on cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/ml. The 1-year patient survival was 83 % in the tacrolimus and 71 % in the cyclosporine group, the 2-year survival rates were 76 % and 66 %, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the cyclosporine group (1.09 episodes). Obliterative bronchiolitis developed in 21.7 % of patients in the tacrolimus group compared with 38.0 % of patients in the cyclosporine group (p = 0.025). Significantly more cyclosporine-treated patients (n = 13) required a switch to tacrolimus than tacrolimus-treated patients to cyclosporine (n = 2) (p = 0.02) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomized to the tacrolimus versus 24 patients to the cyclosporine group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml.

The 1-year survival rates were 73.1 % in the tacrolimus versus 79.2 % in the cyclosporine group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7 % versus 45.8 %) and at 1 year after lung transplantation (50 % versus 33.3 %).

The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

Pancreas transplantation
A multicentre study included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomized to tacrolimus (n=103) or to cyclosporine (n=102). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6.

Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3 % versus 74.5 % with cyclosporine (p < 0.0005), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from cyclosporine to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy.

Intestinal transplantation
Published clinical experience from a single centre on the use of tacrolimus for primary treatment following intestinal transplantation showed that the actuarial survival rate of 155 patients (65 intestine alone, 75 liver and intestine, and 25 multivisceral) receiving tacrolimus and prednisone was 75 % at 1 year, 54 % at 5 years, and 42 % at 10 years. In the early years the initial oral dose of tacrolimus was 0.3 mg/kg/day. Results continuously improved with increasing experience over the course of 11 years. A variety of innovations, such as techniques for early detection of Epstein-Barr (EBV) and CMV infections, bone marrow augmentation, the adjunct use of the interleukin-2 antagonist daclizumab, lower initial tacrolimus doses with target trough levels of 10 to 15 ng/ml, and most recently allograft irradiation were considered to have contributed to improved results in this indication over time.
5.2 Pharmacokinetic properties

Absorption

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus capsules peak concentrations (Cmax) of tacrolimus in blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20 % - 25 %.

After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients. In healthy subjects, tacrolimus 0.5 mg, tacrolimus 1 mg and tacrolimus 5 mg capsules, hard have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34 % of calories) content. Decreases in AUC (27 %) and Cmax (50 %), and an increase in tmax (173 %) in whole blood were evident.

In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12 %) and Cmax (15 to 38 %), and an increase in tmax (38 to 80 %) in whole blood were evident.

Bile flow does not influence the absorption of tacrolimus.

A strong correlation exists between AUC and whole blood trough levels at steady-state. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

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.

Metabolism and biotransformation

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

Excretion

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. 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.

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

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. Embryofetal 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 content:
Povidone K-30
Croscarmellose sodium (E468)
Lactose anhydrous
Magnesium stearate

Miloprosan 5mg Capsule shells:
Titanium dioxide (E171)
Red Iron Oxide (E-172)
Gelatin

6.2 Incompatibilities
Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer a suspension of Miloprosan 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 below 30°C, in the original package, to protect from moisture & light.

6.5 Nature and contents of container
PVC/PVdC-Aluminium blister pack
10 capsules per blister. Blisters placed with a desiccant in an aluminium foil sachet.
Pack sizes:
30, 50, 60, 100 capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
PharOs-Pharmaceutical Oriented Services Ltd
87, Marathonomos Ave & Salaminas Str.
15351 Pallini Attikis
Greece

8 MARKETING AUTHORISATION NUMBER(S)
PL23022/0093

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/01/2012

10 DATE OF REVISION OF THE TEXT
PAR Miloprosan/Tamitect 0.5 mg Hard Capsules
Miloprosan/Tamitect 1 mg Hard Capsules
Miloprosan/Tamitect 5 mg Hard Capsules

19/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Tamitect 0.5 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Tamitect 0.5 mg hard capsule contains 0.5 mg tacrolimus

Excipient(s):
Each Tamitect 0.5 mg hard capsule contains 109.1 mg lactose anhydrous
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Tamitect 0.5 mg hard capsule: Ivory cap and ivory body hard shell capsules with white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

4.2 Posology and method of administration
Tamitect therapy requires careful monitoring by adequately qualified and equipped personnel.
The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated,
by physicians experienced in immunosuppressive therapy and the management of transplanted patients.

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations
of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including
under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to
tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding
daily dosing regimen; alterations in formulation or regimen should only take place under the close
supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative
formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that
systemic exposure to tacrolimus is maintained.

General considerations
The recommended initial dosages presented below are intended to act solely as a guideline. tacrolimus
dosing should primarily be based on clinical assessments of rejection and tolerability in each patient
individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If
clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be
considered.

Tacrolimus can be administered intravenously or orally. In general, dosing may commence orally, if
necessary, by administering the capsule contents suspended in water, via nasogastric tubing.
Tacrolimus is routinely administered in conjunction with other immunosuppressive agents in the initial
post-operative period. The Tamitect dose may vary depending upon the immunosuppressive regimen
chosen.

Method of administration
It is recommended that the oral daily dose be administered in two divided doses (e.g. morning and
evening). Capsules should be taken immediately following removal from the blister. The capsules
should be swallowed with fluid (preferably water).
Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3
hours after a meal, to achieve maximal absorption (see section 5.2).
Patients should be advised not to swallow the desiccant.

Duration of dosing
To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the
duration of oral therapy can be given.
Dosage recommendations – Liver transplantation

Prophylaxis of transplant rejection - adults
Oral tacrolimus therapy should commence at 0.10 - 0.20 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery.
If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 - 0.05 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection - children
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 dosing, an initial intravenous dose of tacrolimus 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Kidney transplantation

Prophylaxis of transplant rejection – adults
Oral tacrolimus therapy should commence at 0.20 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.
If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.05 - 0.10 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection – children
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 dosing, an initial intravenous dose of tacrolimus 0.075 – 0.100 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus-based dualtherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.
Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation
Prophylaxis of transplant rejection – adults
Tacrolimus can be used with antibody induction (allowing for delayed start of tacrolimus therapy) or alternatively in clinically stable patients without antibody induction.
Following antibody induction, oral tacrolimus therapy should commence at a dose of 0.075 mg/kg/day administered as two divided doses (e.g. morning and evening).
Administration should commence within 5 days after the completion of surgery as soon as the patient’s clinical condition is stabilized. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.
An alternative strategy was published where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection – children
Tacrolimus has been used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if tacrolimus therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 – 25 ng/ml.
Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.
Following antibody induction, if tacrolimus therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening).

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. In adult patients converted to tacrolimus, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g. morning and evening).
In paediatric patients converted to tacrolimus, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in two divided doses (e.g. morning and evening).
For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Rejection therapy, other allografts
The dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data. In lung-transplanted patients tacrolimus has been used at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

Dosage adjustments in special populations
Hepatic impairment
Dose reduction may be necessary in patients with severe liver impairment in order to maintain the tacrolimus blood trough levels within the recommended target range.
Renal impairment
As the pharmacokinetics of tacrolimus are unaffected by renal function (see section 5.2), no dose adjustment is required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender: There is no evidence that male and female patients require different doses to achieve similar trough levels.

Paediatric patients
In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

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

Conversion from cyclosporine
Care should be taken when converting patients from cyclosporine-based to tacrolimus based therapy (see sections 4.4 and 4.5). The combined administration of cyclosporine and tacrolimus is not recommended. Tacrolimus therapy should be initiated after considering cyclosporine blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporine blood levels. In practice, tacrolimus therapy has been initiated 12 - 24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued following conversion as the clearance of cyclosporine might be affected.

Therapeutic drug monitoring
Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring. As an aid to optimize dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood including a semi-automated microparticle enzyme immunoassay (MEIA). Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. Blood trough levels of tacrolimus should be monitored during the post-transplantation period. When dosed orally, blood trough levels should be drawn approximately 12 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As Tamitect is a medicinal product with low clearance, adjustments to the dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5).

Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

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

4.3 Contraindications
Hypersensitivity to tacrolimus or other macrolides.
Hypersensitivity to any of the excipients (see section 6.1).
4.4 Special warnings and precautions for use

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, hematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

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

Herbal preparations containing St. John’s Wort (Hypericum perforatum) should be avoided when taking Tamitect due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus (see section 4.5).

The combined administration of cyclosporine and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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.

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 in tacrolimus treated patients 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 9-12 months). If abnormalities develop, dose reduction of tacrolimus, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.

**Lymph proliferative disorders and malignancies**

Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to tacrolimus therapy should not receive antilymphocyte 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. 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 potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

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.

Patients treated with immunosuppressants, including tacrolimus are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). 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 renal function or neurological symptoms.

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Special populations
There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA).

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

Tamitect contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Systemically available tacrolimus is metabolized by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels
Clinically the following substances have been shown to increase tacrolimus blood levels: Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (e.g. ritonavir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided. Lansoprazol and ciclosporine may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

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

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

\textit{CYP3A4 inducers potentially leading to decreased tacrolimus blood levels}
Clinically the following substances have been shown to decrease tacrolimus blood levels: Strong interactions have been observed with rifampicin, phenytoin or St. John’s Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels. Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

\textit{Effect of tacrolimus on the metabolism of other medicinal products}
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolized by CYP3A4 may affect the metabolism of such medicinal products. The half-life of ciclosporine is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporine (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.

\textit{Other interactions leading to clinically detrimental effects}
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole+trimethoprim, NSAIDs, ganciclovir or aciclovir).

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

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

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

\section{4.6 Fertility, Pregnancy and lactation}
Human data show that tacrolimus cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to
the fetus. In case of in utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn, (incidence 8 of 111 neonates, i.e. 7.2%), which, however, normalizes spontaneously. In rats and rabbits, tacrolimus caused embryofetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

**Lactation**

Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving <PRODUCT NAME>.

**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

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Tamitect is administered in association with alcohol. No studies on the effects of tacrolimus on the ability to drive and use machines have been performed.

### 4.8 Undesirable effects

The adverse drug 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 drug reactions stated below are reversible and/or respond to dose reduction. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Cardiac disorders**

common: ischaemic coronary artery disorders, tachycardia

uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal

rare: pericardial effusion

very rare: echocardiogram abnormal

**Blood and lymphatic system disorders**

common: anaemia, leukopenia, thrombocytopenia, leukocytosis red blood cell analyses abnormal,

uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia,

rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

**Nervous system disorders**

very common: headache, tremor

common: seizures, disturbances in consciousness, paraesthesias and dysesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders

uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare: hypertonia
very rare: myasthenia

Eye disorders
common: vision blurred, photophobia, eye disorders
uncommon: cataract
rare: blindness

Ear and labyrinth disorders
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

Respiratory, thoracic and mediastinal disorders
common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis cough, nasal congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome

Gastrointestinal disorders
very common: diarrhoea, nausea
common: 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
uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastro oesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

Renal and urinary disorders
very common: renal impairment
common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhagic

Skin and subcutaneous tissue disorders
common: pruritus, rash, alopecias, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell’s syndrome)
very rare: Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders
common: arthralgia, muscle cramps, pain in limb, back pain,
uncommon: joint disorders

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities,
uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of preexisting infections may be aggravated. Both generalized and localized infections can occur. Cases of 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

Injury, poisoning and procedural complications
common: primary graft dysfunction

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

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 treatment.

Vascular disorders
very common: hypertension
common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock

General disorders and administration site conditions
common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed
uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased.
rare: thirst, fall, ulcer, chest tightness, mobility decreased
very rare: fat tissue increased

Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4).

**Hepatobiliary disorders**
- common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
- rare: hepatitic artery thrombosis, venoocclusive liver disease
- very rare: hepatic failure, bile duct stenosis

**Reproductive system and breast disorders**
- uncommon: dysmenorrhoea and uterine bleeding

**Psychiatric disorders**
- very common: insomnia
- common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders,
- uncommon: psychotic disorder

**4.9 Overdose**
Experience with over dosage is limited. Several cases of accidental over dosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen serum creatinine and increase in alanine aminotransferase levels. No specific antidote to Tamitect therapy is available. If over dosage 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 will not be dialyzable. In isolated patients with very high plasma levels, haemofiltration 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 inhibitor, ATC code: L04AD02

*Mechanism of action*
At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.

Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both *in vitro* and *in vivo* experiments.

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

*Clinical efficacy and safety of tacrolimus capsules bid in primary organ transplantation*
In prospective published studies tacrolimus was investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of tacrolimus in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus was used as primary treatment in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarized below.
Lung transplantation

The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomization to either tacrolimus or cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus cyclosporine-treated patients (11.5 % versus 22.6 %) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86 % versus 8.57 %), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8 % in the tacrolimus and 83 % in the cyclosporine group.

Another randomized study included 66 patients on tacrolimus versus 67 patients on cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/ml. The 1-year patient survival was 83 % in the tacrolimus and 71 % in the cyclosporine group, the 2-year survival rates were 76 % and 66 %, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the cyclosporine group (1.09 episodes). Obliterative bronchiolitis developed in 21.7 % of patients in the tacrolimus group compared with 38.0 % of patients in the cyclosporine group (p = 0.025). Significantly more cyclosporine-treated patients (n = 13) required a switch to tacrolimus than tacrolimus-treated patients to cyclosporine (n = 2) (p = 0.02) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomized to the tacrolimus versus 24 patients to the cyclosporine group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml.

The 1-year survival rates were 73.1 % in the tacrolimus versus 79.2 % in the cyclosporine group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7 % versus 45.8 %) and at 1 year after lung transplantation (50 % versus 33.3 %).

The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

Pancreas transplantation

A multicentre study included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomized to tacrolimus (n=103) or to cyclosporine (n=102). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6.

Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3 % versus 74.5 % with cyclosporine (p < 0.0005), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from cyclosporine to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy.

Intestinal transplantation

Published clinical experience from a single centre on the use of tacrolimus for primary treatment following intestinal transplantation showed that the actuarial survival rate of 155 patients (65 intestine alone, 75 liver and intestine, and 25 multivisceral) receiving tacrolimus and prednisone was 75 % at 1 year, 54 % at 5 years, and 42 % at 10 years. In the early years the initial oral dose of tacrolimus was 0.3 mg/kg/day. Results continuously improved with increasing experience over the course of 11 years. A variety of innovations, such as techniques for early detection of Epstein-Barr (EBV) and CMV infections, bone marrow augmentation, the adjunct use of the interleukin-2 antagonist daclizumab, lower initial tacrolimus doses with target trough levels of 10 to 15 ng/ml, and most recently allograft irradiation were considered to have contributed to improved results in this indication over time.

5.2 Pharmacokinetic properties

Absorption

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus capsules peak concentrations (Cmax) of tacrolimus in
blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20 - 25%.

After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients. In healthy subjects, tacrolimus 0.5 mg, tacrolimus 1 mg and tacrolimus 5 mg capsules, hard have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34 % of calories) content. Decreases in AUC (27 %) and Cmax (50 %), and an increase in tmax (173 %) in whole blood were evident.

In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12 %) and Cmax (15 to 38 %), and an increase in tmax (38 to 80 %) in whole blood were evident.

Bile flow does not influence the absorption of tacrolimus.

A strong correlation exists between AUC and whole blood trough levels at steady-state. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

**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.

**Metabolism and biotransformation**

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

**Excretion**

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. 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.

Following intravenous and oral administration of 14C-labelled tacrolimus, most of the radioactivity was eliminated in the feces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and feces, indicating that tacrolimus is almost completely metabolized prior to elimination: bile being the principal route of elimination.
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. 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 content:
Povidone K-30
Crocarmellose sodium (E468)
Lactose anhydrous
Magnesium stearate

Tamitect 0.5 mg Capsule shells:
Titanium dioxide (E171)
Yellow Iron Oxide (E-172)
Gelatin

6.2 Incompatibilities
Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer a suspension of Tamitect 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 below 30°C, in the original package, to protect from moisture & light.

6.5 Nature and contents of container
PVC/PVdC-Aluminium blister pack
10 capsules per blister. Blisters placed with a desiccant in an aluminium foil sachet.

   Pack sizes:
   7, 10, 14, 20, 28, 30, 50, 60, 100

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
PharOs-Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Salaminas Str.
15351 Pallini Attikis
Greece

8 MARKETING AUTHORISATION NUMBER(S)
PL 23022/0094

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/01/2012

10 DATE OF REVISION OF THE TEXT
19/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Tamitect 1 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Tamitect 1 mg hard capsule contains 1 mg tacrolimus

Excipient(s):
Each Tamitect 1 mg hard capsule contains 108.6 mg lactose anhydrous
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Tamitect 1 mg hard capsule: White cap and white body hard shell capsules with white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

4.2 Posology and method of administration
Tamitect therapy requires careful monitoring by adequately qualified and equipped personnel.
The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated,
by physicians experienced in immunosuppressive therapy and the management of transplanted patients.

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations
of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including
under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to
Tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding
daily dosing regimen; alterations in formulation or regimen should only take place under the close
supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative
formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that
systemic exposure to tacrolimus is maintained.

General considerations
The recommended initial dosages presented below are intended to act solely as a guideline. tacrolimus
dosing should primarily be based on clinical assessments of rejection and tolerability in each patient
individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If
clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be
considered.

Tacrolimus can be administered intravenously or orally. In general, dosing may commence orally, if
necessary, by administering the capsule contents suspended in water, via nasogastric tubing.
Tacrolimus is routinely administered in conjunction with other immunosuppressive agents in the initial
post-operative period. The Tamitect dose may vary depending upon the immunosuppressive regimen
chosen.

Method of administration
It is recommended that the oral daily dose be administered in two divided doses (e.g. morning and
evening). Capsules should be taken immediately following removal from the blister. The capsules
should be swallowed with fluid (preferably water).
Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3
hours after a meal, to achieve maximal absorption (see section 5.2).
Patients should be advised not to swallow the desiccant.

Duration of dosing
To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the
duration of oral therapy can be given.
**Dosage recommendations – Liver transplantation**

*Prophylaxis of transplant rejection - adults*

Oral tacrolimus therapy should commence at 0.10 - 0.20 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 - 0.05 mg/kg/day should be initiated as a continuous 24-hour infusion.

*Prophylaxis of transplant rejection - children*

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 dosing, an initial intravenous dose of tacrolimus 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.

**Dose adjustment during post-transplant period in adults and children**

Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

*Rejection therapy – adults and children*

Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.

For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

*Rejection therapy – adults and children*

Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.

For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

**Dosage recommendations - Kidney transplantation**

*Prophylaxis of transplant rejection – adults*

Oral tacrolimus therapy should commence at 0.20 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.05 - 0.10 mg/kg/day should be initiated as a continuous 24-hour infusion.

*Prophylaxis of transplant rejection – children*

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 dosing, an initial intravenous dose of tacrolimus 0.075 – 0.100 mg/kg/day should be administered as a continuous 24-hour infusion.

**Dose adjustment during post-transplant period in adults and children**

Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus-based dualtherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.
Rejection therapy – adults and children

Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.

For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation

Prophylaxis of transplant rejection – adults

Tacrolimus can be used with antibody induction (allowing for delayed start of tacrolimus therapy) or alternatively in clinically stable patients without antibody induction.

Following antibody induction, oral tacrolimus therapy should commence at a dose of 0.075 mg/kg/day administered as two divided doses (e.g. morning and evening).

Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilized. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.

An alternative strategy was published where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection – children

Tacrolimus has been used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if tacrolimus therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 – 25 ng/ml.

Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.

Following antibody induction, if tacrolimus therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening).

Dose adjustment during post-transplant period in adults and children

Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children

Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. In adult patients converted to tacrolimus, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g. morning and evening).

In paediatric patients converted to tacrolimus, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in two divided doses (e.g. morning and evening).

For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Rejection therapy, other allografts

The dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data. In lung-transplanted patients tacrolimus has been used at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

Dosage adjustments in special populations

Hepatic impairment

Dose reduction may be necessary in patients with severe liver impairment in order to maintain the tacrolimus blood trough levels within the recommended target range.
Renal impairment
As the pharmacokinetics of tacrolimus are unaffected by renal function (see section 5.2), no dose adjustment is required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender: There is no evidence that male and female patients require different doses to achieve similar trough levels.

Paediatric patients
In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

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

Conversion from cyclosporine
Care should be taken when converting patients from cyclosporine-based to tacrolimus based therapy (see sections 4.4 and 4.5). The combined administration of cyclosporine and tacrolimus is not recommended. Tacrolimus therapy should be initiated after considering cyclosporine blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporine blood levels. In practice, tacrolimus therapy has been initiated 12 - 24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued following conversion as the clearance of cyclosporine might be affected.

Therapeutic drug monitoring
Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring. As an aid to optimize dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood including a semi-automated microparticle enzyme immunoassay (MEIA). Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. Blood trough levels of tacrolimus should be monitored during the post-transplantation period. When dosed orally, blood trough levels should be drawn approximately 12 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As Tamitect is a medicinal product with low clearance, adjustments to the dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5).

Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

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

4.3 Contraindications
Hypersensitivity to tacrolimus or other macrolides.
Hypersensitivity to any of the excipients (see section 6.1).
4.4 Special warnings and precautions for use

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, hematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

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

Herbal preparations containing St. John’s Wort (Hypericum perforatum) should be avoided when taking Tamitect due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus (see section 4.5).

The combined administration of cyclosporine and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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.

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 in tacrolimus treated patients 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 9-12 months). If abnormalities develop, dose reduction of tacrolimus, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.

Lymph proliferative disorders and malignancies

Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to tacrolimus therapy should not receive antilymphocyte 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. 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 potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

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.

Patients treated with immunosuppressants, including tacrolimus are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). 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 renal function or neurological symptoms.

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Special populations
There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA).

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

Tamitect contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Systemically available tacrolimus is metabolized by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels
Clinically the following substances have been shown to increase tacrolimus blood levels: Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (e.g. ritonavir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltilazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisons, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided. Lansoprazol and ciclosporine may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

Other interactions potentially leading to increased tacrolimus blood levels
Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics).
Other potential interactions that may increase systemic exposure of tacrolimus include prokinetic agents (such as metoclopramide and cisapride), cimetidine and magnesiumaluminium-hydroxide.

**CYP3A4 inducers potentially leading to decreased tacrolimus blood levels**
Clinically the following substances have been shown to decrease tacrolimus blood levels: Strong interactions have been observed with rifampicin, phenytoin or St. John’s Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.
Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

**Effect of tacrolimus on the metabolism of other medicinal products**
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolized by CYP3A4 may affect the metabolism of such medicinal products. The half-life of ciclosporine is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporine (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 phenazone.

**Other interactions leading to clinically detrimental effects**
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole+trimethoprim, NSAIDs, ganciclovir or aciclovir).

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

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

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

### 4.6 Fertility, Pregnancy and lactation

Human data show that tacrolimus cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to
the fetus. In case of in utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn, (incidence 8 of 111 neonates, i.e. 7.2%), which, however, normalizes spontaneously. In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

**Lactation**

Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving PAR Miloprosan/Tamitect.

**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**

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Tamitect is administered in association with alcohol. No studies on the effects of tacrolimus on the ability to drive and use machines have been performed

4.8 **Undesirable effects**

The adverse drug 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 drug reactions stated below are reversible and/or respond to dose reduction. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Cardiac disorders**

common: ischaemic coronary artery disorders, tachycardia

uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal

rare: pericardial effusion

very rare: echocardiogram abnormal

**Blood and lymphatic system disorders**

common: anaemia, leukopenia, thrombocytopenia, leukocytosis red blood cell analyses abnormal,

uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia,

rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

**Nervous system disorders**

very common: headache, tremor

common: seizures, disturbances in consciousness, paraesthesias and dysesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders

uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare: hypertonia
very rare: myasthenia

**Eye disorders**
common: vision blurred, photophobia, eye disorders
uncommon: cataract
rare: blindness

**Ear and labyrinth disorders**
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

**Respiratory, thoracic and mediastinal disorders**
common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis cough, nasal congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome

**Gastrointestinal disorders**
very common: diarrhoea, nausea
common: 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
uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastro oesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

**Renal and urinary disorders**
very common: renal impairment
common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhagic

**Skin and subcutaneous tissue disorders**
common: pruritus, rash, alopecias, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell’s syndrome)
very rare: Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders
common: arthralgia, muscle cramps, pain in limb, back pain,
uncommon: joint disorders

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities,
uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of preexisting infections may be aggravated. Both generalized and localized infections can occur. Cases of 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

Injury, poisoning and procedural complications
common: primary graft dysfunction

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

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 treatment.

Vascular disorders
very common: hypertension
common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock

General disorders and administration site conditions
common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed
uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased.
rare: thirst, fall, ulcer, chest tightness, mobility decreased
very rare: fat tissue increased

Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4).

**Hepatobiliary disorders**
- **common:** hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
- **rare:** hepatitis artery thrombosis, venoocclusive liver disease
- **very rare:** hepatic failure, bile duct stenosis

**Reproductive system and breast disorders**
- **uncommon:** dysmenorrhoea and uterine bleeding

**Psychiatric disorders**
- **very common:** insomnia
- **common:** anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders,
- **uncommon:** psychotic disorder

4.9 Overdose
Experience with over dosage is limited. Several cases of accidental over dosage have been reported; symptoms have included tremor, headache, nausea and vomiting, urticaria, lethargy and increases in blood urea nitrogen serum creatinine and increase in alanine aminotransferase levels. No specific antidote to Tamitect therapy is available. If over dosage 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 will not be dialyzable. In isolated patients with very high plasma levels, haemofiltration 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 inhibitor, ATC code: L04AD02

*Mechanism of action*
At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKB P12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.

Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both *in vitro* and *in vivo* experiments.

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

*Clinical efficacy and safety of tacrolimus capsules bid in primary organ transplantation*
In prospective published studies tacrolimus was investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of tacrolimus in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus was used as primary treatment in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarized below.
**Lung transplantation**

The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomization to either tacrolimus or cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus cyclosporine-treated patients (11.5 % versus 22.6 %) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86 % versus 8.57 %), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8 % in the tacrolimus and 83 % in the cyclosporine group.

Another randomized study included 66 patients on tacrolimus versus 67 patients on cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/ml. The 1-year patient survival was 83 % in the tacrolimus and 71 % in the cyclosporine group, the 2-year survival rates were 76 % and 66 %, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the cyclosporine group (1.09 episodes). Obliterative bronchiolitis developed in 21.7 % of patients in the tacrolimus group compared with 38.0 % of patients in the cyclosporine group (p = 0.025). Significantly more cyclosporine-treated patients (n = 13) required a switch to tacrolimus than tacrolimus-treated patients to cyclosporine (n = 2) (p = 0.02) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomized to the tacrolimus versus 24 patients to the cyclosporine group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml.

The 1-year survival rates were 73.1 % in the tacrolimus versus 79.2 % in the cyclosporine group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7 % versus 45.8 %) and at 1 year after lung transplantation (50 % versus 33.3 %).

The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

**Pancreas transplantation**

A multicentre study included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomized to tacrolimus (n=103) or to cyclosporine (n=102). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6.

Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3 % versus 74.5 % with cyclosporine (p < 0.0005), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from cyclosporine to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy.

**Intestinal transplantation**

Published clinical experience from a single centre on the use of tacrolimus for primary treatment following intestinal transplantation showed that the actuarial survival rate of 155 patients (65 intestine alone, 75 liver and intestine, and 25 multivisceral) receiving tacrolimus and prednisone was 75 % at 1 year, 54 % at 5 years, and 42 % at 10 years. In the early years the initial oral dose of tacrolimus was 0.3 mg/kg/day. Results continuously improved with increasing experience over the course of 11 years. A variety of innovations, such as techniques for early detection of Epstein-Barr (EBV) and CMV infections, bone marrow augmentation, the adjunct use of the interleukin-2 antagonist daclizumab, lower initial tacrolimus doses with target trough levels of 10 to 15 ng/ml, and most recently allograft irradiation were considered to have contributed to improved results in this indication over time.

### 5.2 Pharmacokinetic properties

**Absorption**

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus capsules peak concentrations (Cmax) of tacrolimus in

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blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20 % - 25 %.

After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients. In healthy subjects, tacrolimus 0.5 mg, tacrolimus 1 mg and tacrolimus 5 mg capsules, hard have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34 % of calories) content. Decreases in AUC (27 %) and Cmax (50 %), and an increase in tmax (173 %) in whole blood were evident. In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12 %) and Cmax (15 to 38 %), and an increase in tmax (38 to 80 %) in whole blood were evident.

Bile flow does not influence the absorption of tacrolimus.

A strong correlation exists between AUC and whole blood trough levels at steady-state. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

**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.

**Metabolism and biotransformation**

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

**Excretion**

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. 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.

Following intravenous and oral administration of 14C-labelled tacrolimus, most of the radioactivity was eliminated in the feces. Approximately 2 % of the radioactivity was eliminated in the urine. Less than 1 % of unchanged tacrolimus was detected in the urine and feces, indicating that tacrolimus is almost completely metabolized prior to elimination: bile being the principal route of elimination.
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. Embryofetal 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 content:
Povidone K-30
Croscarmellose sodium (E468)
Lactose anhydrous
Magnesium stearate

Tamitect 1 mg Capsule shells:
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities
Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer a suspension of Tamitect 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 below 30°C, in the original package, to protect from moisture & light.

6.5 Nature and contents of container
PVC/PVdC-Aluminium blister pack
10 capsules per blister. Blisters placed with a desiccant in an aluminium foil sachet.

Pack sizes:
7, 10, 14, 20, 28, 30, 50, 60, 100
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORIZATION HOLDER
PharOs-Pharmaceutical Oriented Services Ltd
87, Marathonomos Ave & Salaminas Str.
15351 Pallini Attikis
Greece

8 MARKETING AUTHORIZATION NUMBER(S)
PL23022/0095

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/01/2012

10 DATE OF REVISION OF THE TEXT
19/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Tamitect 5.0 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Tamitect 5 mg hard capsule contains 5 mg tacrolimus

Excipient(s):
Each Tamitect 5.0 mg hard capsule contains 104.6 mg lactose anhydrous
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Tamitect 1 mg hard capsule: 5 mg hard capsule: Red cap and red body hard shell capsules with white powder

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

4.2 Posology and method of administration
Tamitect therapy requires careful monitoring by adequately qualified and equipped personnel.
The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplanted patients.

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

General considerations
The recommended initial dosages presented below are intended to act solely as a guideline. tacrolimus dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

Tacrolimus can be administered intravenously or orally. In general, dosing may commence orally, if necessary, by administering the capsule contents suspended in water, via nasogastric tubing. Tacrolimus is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The Tamitect dose may vary depending upon the immunosuppressive regimen chosen.

Method of administration
It is recommended that the oral daily dose be administered in two divided doses (e.g. morning and evening). Capsules should be taken immediately following removal from the blister. The capsules should be swallowed with fluid (preferably water).
Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption (see section 5.2). Patients should be advised not to swallow the desiccant.

Duration of dosing
To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the duration of oral therapy can be given.
Dosage recommendations – Liver transplantation

Prophylaxis of transplant rejection - adults
Oral tacrolimus therapy should commence at 0.10 - 0.20 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 - 0.05 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection - children
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 dosing, an initial intravenous dose of tacrolimus 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.

For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.

For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Kidney transplantation

Prophylaxis of transplant rejection – adults
Oral tacrolimus therapy should commence at 0.20 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.05 - 0.10 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection – children
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 dosing, an initial intravenous dose of tacrolimus 0.075 – 0.100 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus-based dualtherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.
Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g. pronounced adverse reactions - see section 4.8) the dose of tacrolimus may need to be reduced.
For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation
Prophylaxis of transplant rejection – adults
Tacrolimus can be used with antibody induction (allowing for delayed start of tacrolimus therapy) or alternatively in clinically stable patients without antibody induction.
Following antibody induction, oral tacrolimus therapy should commence at a dose of 0.075 mg/kg/day administered as two divided doses (e.g. morning and evening).
Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilized. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of tacrolimus 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.
An alternative strategy was published where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection – children
Tacrolimus has been used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if tacrolimus therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 – 25 ng/ml.
Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.
Following antibody induction, if tacrolimus therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening).

Dose adjustment during post-transplant period in adults and children
Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy – adults and children
Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. In adult patients converted to tacrolimus, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g. morning and evening).
In paediatric patients converted to tacrolimus, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in two divided doses (e.g. morning and evening).
For information on conversion from cyclosporine to Tamitect, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Rejection therapy, other allografts
The dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data. In lung-transplanted patients tacrolimus has been used at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

Dosage adjustments in special populations
Hepatic impairment
Dose reduction may be necessary in patients with severe liver impairment in order to maintain the tacrolimus blood trough levels within the recommended target range.
Renal impairment
As the pharmacokinetics of tacrolimus are unaffected by renal function (see section 5.2), no dose adjustment is required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender: There is no evidence that male and female patients require different doses to achieve similar trough levels.

Paediatric patients
In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

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

Conversion from cyclosporine
Care should be taken when converting patients from cyclosporine-based to tacrolimus based therapy (see sections 4.4 and 4.5). The combined administration of cyclosporine and tacrolimus is not recommended. Tacrolimus therapy should be initiated after considering cyclosporine blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporine blood levels. In practice, tacrolimus therapy has been initiated 12 - 24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued following conversion as the clearance of cyclosporine might be affected.

Therapeutic drug monitoring
Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring. As an aid to optimize dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood including a semi-automated microparticle enzyme immunoassay (MEIA). Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. Blood trough levels of tacrolimus should be monitored during the post-transplantation period. When dosed orally, blood trough levels should be drawn approximately 12 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As Tamitect is a medicinal product with low clearance, adjustments to the dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5).

Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

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

4.3 Contraindications
Hypersensitivity to tacrolimus or other macrolides.
Hypersensitivity to any of the excipients (see section 6.1).
4.4 Special warnings and precautions for use

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, hematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

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

Herbal preparations containing St. John’s Wort (Hypericum perforatum) should be avoided when taking Tamitect due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus (see section 4.5).

The combined administration of cyclosporine and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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.

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 in tacrolimus treated patients 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 9-12 months). If abnormalities develop, dose reduction of tacrolimus, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.

**Lymph proliferative disorders and malignancies**

Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to tacrolimus therapy should not receive antilymphocyte 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. 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 potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

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.

Patients treated with immunosuppressants, including tacrolimus are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). 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 renal function or neurological symptoms.

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised.

Most patients completely recover after appropriate measures are taken.

Special populations
There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA).

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

Tamitect contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Systemically available tacrolimus is metabolized by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels
Clinically the following substances have been shown to increase tacrolimus blood levels: Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (e.g. ritonavir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided. Lansoprazol and cyclosporine may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

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

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

**CYP3A4 inducers potentially leading to decreased tacrolimus blood levels**
Clinically the following substances have been shown to decrease tacrolimus blood levels: Strong interactions have been observed with rifampicin, phenytoin or St. John’s Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.
Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

**Effect of tacrolimus on the metabolism of other medicinal products**
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolized by CYP3A4 may affect the metabolism of such medicinal products. The half-life of cyclosporine is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (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 phenazone.

**Other interactions leading to clinically detrimental effects**
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole-trimethoprim, NSAIDs, ganciclovir or aciclovir).

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

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

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

### 4.6 Fertility, Pregnancy and lactation

Human data show that tacrolimus cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to
the fetus. In case of in utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn, (incidence 8 of 111 neonates, i.e. 7.2%), which, however, normalizes spontaneously. In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

Lactation
Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving <PRODUCT NAME>.

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
Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Tamitect is administered in association with alcohol. No studies on the effects of tacrolimus on the ability to drive and use machines have been performed.

4.8 Undesirable effects
The adverse drug 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 drug reactions stated below are reversible and/or respond to dose reduction. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders
common: ischaemic coronary artery disorders, tachycardia
uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal
rare: pericardial effusion
very rare: echocardiogram abnormal

Blood and lymphatic system disorders
common: anaemia, leukopenia, thrombocytopenia, leukocytosis red blood cell analyses abnormal,
uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia,
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

Nervous system disorders
very common: headache, tremor
common: seizures, disturbances in consciousness, paraesthesias and dysesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders
uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare: hypertonia
very rare: myasthenia

Eye disorders
common: vision blurred, photophobia, eye disorders
uncommon: cataract
rare: blindness

Ear and labyrinth disorders
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

Respiratory, thoracic and mediastinal disorders
common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis cough, nasal congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome

Gastrointestinal disorders
very common: diarrhoea, nausea
common: 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
uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastro oesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

Renal and urinary disorders
very common: renal impairment
common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhagic

Skin and subcutaneous tissue disorders
common: pruritus, rash, alopecias, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell’s syndrome)
very rare: Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders
common: arthralgia, muscle cramps, pain in limb, back pain,
uncommon: joint disorders

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities,
uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of preexisting infections may be aggravated. Both generalized and localized infections can occur. Cases of 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

Injury, poisoning and procedural complications
common: primary graft dysfunction

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

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 treatment.

Vascular disorders
very common: hypertension
common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders
vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock

General disorders and administration site conditions
common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed
uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased.
rare: thirst, fall, ulcer, chest tightness, mobility decreased
very rare: fat tissue increased
Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4).

Hepatobiliary disorders
common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis

rare: hepatitic artery thrombosis, venoocclusive liver disease

very rare: hepatic failure, bile duct stenosis

Reproductive system and breast disorders
uncommon: dysmenorrhoea and uterine bleeding

Psychiatric disorders
very common: insomnia

common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders,

uncommon: psychotic disorder

4.9 Overdose
Experience with over dosage is limited. Several cases of accidental over dosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen serum creatinine and increase in alanine aminotransferase levels.

No specific antidote to Tamitect therapy is available. If over dosage 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 will not be dialyzable. In isolated patients with very high plasma levels, haemofiltration 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 inhibitor, ATC code: L04AD02

Mechanism of action
At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.

Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both in vitro and in vivo experiments.

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

Clinical efficacy and safety of tacrolimus capsules bid in primary organ transplantation
In prospective published studies tacrolimus was investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of tacrolimus in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus was used as primary treatment in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarized below.


**Lung transplantation**

The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomization to either tacrolimus or cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus cyclosporine-treated patients (11.5 % versus 22.6 %) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86 % versus 8.57 %), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8 % in the tacrolimus and 83 % in the cyclosporine group.

Another randomized study included 66 patients on tacrolimus versus 67 patients on cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/ml. The 1-year patient survival was 83 % in the tacrolimus and 71 % in the cyclosporine group, the 2-year survival rates were 76 % and 66 %, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the cyclosporine group (1.09 episodes). Obliterative bronchiolitis developed in 21.7 % of patients in the tacrolimus group compared with 38.0 % of patients in the cyclosporine group (p = 0.025). Significantly more cyclosporine-treated patients (n = 13) required a switch to tacrolimus than tacrolimus-treated patients to cyclosporine (n = 2) (p = 0.02) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomized to the tacrolimus versus 24 patients to the cyclosporine group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml.

The 1-year survival rates were 73.1 % in the tacrolimus versus 79.2 % in the cyclosporine group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7 % versus 45.8 %) and at 1 year after lung transplantation (50 % versus 33.3 %).

The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

**Pancreas transplantation**

A multicentre study included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomized to tacrolimus (n=103) or to cyclosporine (n=102). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6.

Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3 % versus 74.5 % with cyclosporine (p < 0.0005), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from cyclosporine to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy.

**Intestinal transplantation**

Published clinical experience from a single centre on the use of tacrolimus for primary treatment following intestinal transplantation showed that the actuarial survival rate of 155 patients (65 intestine alone, 75 liver and intestine, and 25 multivisceral) receiving tacrolimus and prednisone was 75 % at 1 year, 54 % at 5 years, and 42 % at 10 years. In the early years the initial oral dose of tacrolimus was 0.3 mg/kg/day. Results continuously improved with increasing experience over the course of 11 years. A variety of innovations, such as techniques for early detection of Epstein-Barr (EBV) and CMV infections, bone marrow augmentation, the adjunct use of the interleukin-2 antagonist daclizumab, lower initial tacrolimus doses with target trough levels of 10 to 15 ng/ml, and most recently allograft irradiation were considered to have contributed to improved results in this indication over time.
5.2 Pharmacokinetic properties

Absorption
In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus capsules peak concentrations (Cmax) of tacrolimus in blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20 % - 25 %.

After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients.

In healthy subjects, tacrolimus 0.5 mg, tacrolimus 1 mg and tacrolimus 5 mg capsules, hard have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34 % of calories) content. Decreases in AUC (27 %) and Cmax (50 %), and an increase in tmax (173 %) in whole blood were evident.

In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12 %) and Cmax (15 to 38 %), and an increase in tmax (38 to 80 %) in whole blood were evident.

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

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.

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

Excretion
Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. 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.

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

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. Embryofetal 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 content:
Povidone K-30
Croscarmellose sodium (E468)
Lactose anhydrous
Magnesium stearate

Tamitect 5mg Capsule shells:
Titanium dioxide (E171)
Red Iron Oxide (E-172)
Gelatin

6.2 Incompatibilities
Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer a suspension of Tamitect 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 below 30°C, in the original package, to protect from moisture & light.

6.5 Nature and contents of container
PVC/PVdC-Aluminium blister pack
10 capsules per blister. Blisters placed with a desiccant in an aluminium foil sachet.
Pack sizes:
7, 10, 14, 20, 28, 30, 50, 60, 100
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
PharOs-Pharmaceutical Oriented Services Ltd
87, Marathonomos Ave & Salaminas Str.
15351 Pallini Attikis
Greece

8 MARKETING AUTHORISATION NUMBER(S)
PL23022/0096

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/01/2012

10 DATE OF REVISION OF THE TEXT
Module 3
Product Information Leaflets

Please note that there are no mock-ups available for PL 23022/0091-3 therefore the leaflets shown are for PL 23022/0094-6 only. The marketing authorisation holder has stated that it does not intend to market the products for PL 23022/0091-3 and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL mock-ups for PL 23022/0091-3 for review to the regulatory authority before marketing the products.

PACKAGING LEAFLET: INFORMATION FOR THE USER
Tamitect 0.5 mg hard capsules
Tacrolimus

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Tamitect is and what it is used for
2. Before you take Tamitect
3. How to take Tamitect
4. Possible side effects
5. How to store Tamitect
6. Further information

1. WHAT TAMICTECT IS AND WHAT IT IS USED FOR
Tamitect is an immunosuppressant. Following your organ transplant (e.g. liver, kidney, heart), your body’s immune system will try to reject the new organ. Tamitect is used to control your body’s immune response enabling your body to accept the transplanted organ.
Tamitect is often used in combination with other medicines that also suppress the immune system.
You may also be given Tamitect for an ongoing rejection of your transplanted liver, kidney, heart or other organ when any previous treatment you were taking was unable to control this immune response after your transplantation.

2. BEFORE YOU TAKE TAMICTECT
Do not take Tamitect
- If you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Tamitect. (See section 6)
- If you are allergic (hypersensitive) to sirolimus or to any macrolide antibiotic (e.g. erythromycin, clarithromycin, josamycin).

Take special care with Tamitect
Tell your doctor if any of the following apply to you:
- If you are taking any medicines mentioned below under 'Using other medicines'.
- If you have or have had liver problems
- If you have diarrhoea for more than one day
- If you need to receive any vaccinations

Your doctor may need to adjust your dose of Tamitect.
You should keep in regular contact with your doctor. From time to time, your doctor may need to do blood, urine, heart, eye tests, to set the right dose of Tamitect.
You should limit your exposure to the sun and UV (ultraviolet) light whilst taking Tamitect. This is because immunosuppressants could increase the risk of skin cancer. Wear appropriate protective clothing and use a sunscreen with a high sun protection factor.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal preparations. Tamitect must not be taken with cyclosporine.
Tamitect blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Tamitect which may require an increase or decrease in dose. In particular, you should tell your doctor if you are taking or have recently taken medicines like:
- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections, such as ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, erythromycin, clarithromycin, josamycin, and rifampicin
- HIV medicines (e.g. ritonavir), used to treat HIV infection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazol or cimetidine)
- antiepileptics, used to treat nausea and vomiting (e.g. metoclopramide)
- cisapride or the antibiotic magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill or other hormone treatments with ethinylestradiol, hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g. nifedipine, nicardipine, diltiazem and verapamil)
- medicines known as "statins" used to treat elevated cholesterol and triglycerides
- phenytoin or phenobarbital, used to treat epilepsy
- the corticosteroids prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression
- Herbal preparations containing St John’s Wort (Hypericum perforatum)


Tell your doctor if you are taking or need to take ibuprofen, amphotericin B or antivirals (e.g. aciclovir). These may worsen kidney or nervous system problems when taken together with Tamitect.

Your doctor also needs to know if you are taking potassium supplements or certain diuretics used for heart failure, hypertension and kidney disease, (e.g. amiloride, triamterene, or spironolactone), non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes, while you take Tamitect.

If you need vaccinations, tell your doctor in advance that you are taking this medicine.

**Taking Tamitect with food and drink**
Take Tamitect on an empty stomach or 2 to 3 hours after a meal. Wait at least 1 hour until the next meal. Avoid grapefruit (also as juice) while on treatment with Tamitect since it can affect its levels.

**Pregnancy and breastfeeding**
If you are, think you might be, or are planning to become pregnant, ask your doctor or pharmacist for advice before taking any medicine. Tacrolimus passes into breast milk. Therefore you should not breast-feed whilst using Tamitect.

**Driving and using machines**
Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking this medicine. These effects are more frequently observed if you also drink alcohol.

**Important information about some of the ingredients of Tamitect**
Tamitect contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

**3. HOW TO TAKE TAMICTECT**
Always take Tamitect exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine.

This medicine should be taken twice a day. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial doses just after transplantation will generally be in the range of 0.075 – 0.30 mg per kg body weight per day depending on the transplanted organ.

Your dose depends on your general condition and on which other immunosuppressive medication you are taking. Regular blood tests by your doctor will be required to define the correct dose and to adjust the dose from time to time. Your doctor will usually reduce your tacrolimus capsules dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take and how often.

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

**If you take more Tamitect than you should**
If you have accidentally taken too much see your doctor or contact your nearest hospital emergency department immediately.

**If you forget to take Tamitect**
Do not take a double dose to make up for forgotten individual doses.

If you have forgotten to take your capsules, wait until it is time for the next dose, and then continue as before.

**If you stop taking Tamitect**
Stopping your treatment may increase the risk of rejection of your transplanted organ. Do not stop your treatment unless your doctor tells you to do so.

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

**4. POSSIBLE SIDE EFFECTS**
Like all medicines, Tamitect can cause side effects, although not everybody gets them.

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

Severe effects may occur, including allergic and anaphylactic reactions. Benign and malignant tumours have been reported following treatment as a result of immunosuppression.

Possible side effects are listed according to the following categories:

Very common side effects are experienced in more than one in ten patients.

Common side effects are experienced in less than one in ten patients but in more than one per one hundred patients.

Uncommon side effects are experienced in less than one in one hundred patients but more than one per one thousand patients.

Rare side effects are experienced in less than one per one thousand patients but more than one per ten thousand patients.

Very rare side effects are experienced in less than one per ten thousand patients.
Very common side effects
- increased blood sugar, diabetes mellitus, increased potassium in the blood
- difficulty in sleeping
- trembling, headache
- increased blood pressure
- diarrhoea, nausea
- kidney problems

Common side effects
- reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts
- reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts (seen in blood tests)
- anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- blurred vision, increased sensitivity to light, eye disorders
- ringing sound in your ears
- reduced blood flow in the heart vessels, faster heartbeat
- bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- shortness in breath, changes in the lung tissue, collection of liquid around the lung, inflammation of the throat, cough, flu-like symptoms
- inflammations or ulcers causing abdominal pain or diarrhoea, bleedings in the stomach, inflammations or ulcers in the mouth, collection of fluid in the belly, vomiting, abdominal pains, indigestion, constipation, passing wind, bloating, loose stools, stomach problems
- changes in liver enzymes and function, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- itching, rash, hair loss, acne, increased sweating
- pain in joints, limbs or back, muscle cramps
- insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- general weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling feverish
- insufficient function of your transplanted organ

Uncommon side effects
- changes in blood clotting, reduction in the number of all types of blood cells
- dehydration, reduced protein or sugar in the blood, increased phosphate in the blood.
- coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- clouding of the eyes
- impaired hearing
- irregular heartbeat, skipped heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
- blood clot in a vein of a limb, shock
- difficulties in breathing, respiratory tract disorders, asthma
- obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
- dermatitis, burning sensation in the sunlight
- joint disorders
- inability to urinate, painful menstruation and abnormal menstrual bleedings
- failure of some organs, influenza like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jitters or abnormal feeling, increase of the enzyme lactate dehydrogenase in your blood, weight loss
Rare side effects
- small bleedings in your skin due to blood clots
- increased muscle stiffness
- blindness
- deafness
- collection of fluid around the heart
- acute breathlessness
- cyst formation in your pancreas
- problems with blood flow in the liver
- serious illness with blistering of skin, mouth, eyes and genitals, increased hairiness
- thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer

Very rare side effects
- muscular weakness
- abnormal heart scan
- liver failure, narrowing of the bile vessel
- painful urination with blood in the urine
- increase of fat tissue

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TAMICTECT
- Keep out of the reach and sight of children.
- Store below 30°C
- Store in the original package (within the foil pouch) in order to protect from moisture & light.
- Do not use Tamictect after the expiry date which is stated on the carton and blister after {EXP}. Once the foil pouch is opened, the product should be used within 1 year. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Tamictect contains
Tamictect 0.5 mg hard capsules
The active substance is tacrolimus.
For 0.5mg: Each capsule contains 0.5mg of tacrolimus
The other ingredients are:
- Capsule content: Povidone K-30, Croscarmellose Sodium (E 468), Lactose anhydrous, Magnesium stearate.
- Capsule shell: Titanium dioxide (E-171), Yellow Iron Oxide (E-172), Gelatin

What Tamictect looks like and contents of the pack
Tamictect 0.5 mg hard capsules
Ivory cap and ivory body hard shell capsules with white powder.
Tamictect 0.5 mg hard capsules are supplied as blister strips containing 10 capsules within a protective foil wrapper, including a desiccant protecting the capsules from moisture. The desiccant should not be swallowed.
Tamictect is available in blister packs containing blister strips of 10 capsules each. 7, 10, 14, 20, 28, 30, 50, 60, 100 capsules.

Marketing Authorization Holder
PharOS – Pharmaceutical Oriented Services Ltd
87, Marathonas Ave & Salaminas str.
15351 Pallini-Attikis
Greece

Manufacturer
Laboratorios Cirfa, S.A.
Olaz-Chipi, 10-Políg Amta 31620 Huarte-Pamplona, Navarra, Spain

midom GmbH Arzneimittel
Mönchener Straße 15, 06796 Brehna, Germany

SUN-FARM Sp. z o.o.
Czerekówka 75, 05-340 Kółbiel, Poland

<This medicinal product is authorized in the Member States of the EEA under the following names:>
UK: Tamictect 0.5mg hard capsules
AT: Tacroctect 0.5mg Hartkapseln
DE: Tacroctect 0.5mg Hartkapseln
PL: Tacroctec 0.5mg Kapsułki, Twarda

This leaflet was last approved in 11/2011
**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Tamitect 1 mg hard capsules**

**Tacrolimus**

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Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. **What Tamitect is and what it is used for**
2. **Before you take Tamitect**
3. **How to take Tamitect**
4. **Possible side effects**
5. **How to store Tamitect**
6. **Further information**

**1. WHAT TAMTECT IS AND WHAT IT IS USED FOR**

Tamitect is an immunosuppressant. Following your organ transplant (e.g. liver, kidney, heart), your body’s immune system will try to reject the new organ. Tamitect is used to control your body’s immune response enabling your body to accept the transplanted organ.

Tamitect is often used in combination with other medicines that also suppress the immune system.

You may also be given Tamitect for an ongoing rejection of your transplanted liver, kidney, heart or other organ when any previous treatment you were taking was unable to control this immune response after your transplantation.

**2. BEFORE YOU TAKE TAMTECT**

**Do not take Tamitect**
- If you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Tamitect. (See section 6)
- If you are allergic (hypersensitive) to sirolimus or to any macrolide antibiotic (e.g. erythromycin, clarithromycin, josamycin).

**Take special care with Tamitect**
Tell your doctor if any of the following apply to you:
- if you are taking any medicines mentioned below under ‘Using other medicines’.
- if you have or have had liver problems
- if you have diarrhea for more than one day
- if you need to receive any vaccinations

Your doctor may need to adjust your dose of Tamitect.
You should keep in regular contact with your doctor. From time to time, your doctor may need to do blood, urine, heart, eye tests, to set the right dose of Tamitect.
You should limit your exposure to the sun and UV (ultraviolet) light whilst taking Tamitect. This is because immunosuppressants could increase the risk of skin cancer. Wear appropriate protective clothing and use a sunscreen with a high sun protection factor.

**Using other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal preparations. Tamitect must not be taken with cyclosporine.

Tamitect blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Tamitect which may require an increase or decrease in dose. In particular, you should tell your doctor if you are taking or have recently taken medicines like:

- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections, such as ketoconazole, fluconazole, itraconazole, voriconazole, clindamycin, erythromycin, clarithromycin, josamycin, and rifampicin
- HIV medicines (e.g. ritonavir), used to treat HIV infection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cinetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- cisapride or the antacid magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill or other hormone treatments with ethinylestradiol, hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g. nifedipine, nisoldipine, diltiazem and verapamil)
- medicines known as “statins” used to treat elevated cholesterol and triglycerides
- phenytion or phenobarbital, used to treat epilepsy
- the corticosteroids prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression
- Herbal preparations containing St. John’s Wort (Hypericum perforatum)
Tell your doctor if you are taking or need to take ibuprofen, amphotericin B or antivirals (e.g. aciclovir). These may worsen kidney or nervous system problems when taken together with Tamitect.

Your doctor also needs to know if you are taking potassium supplements or certain diuretics used for heart failure, hypertension and kidney disease, (e.g. amiloride, triamterene, or spironolactone), non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes, while you take Tamitect.

If you need vaccinations, tell your doctor in advance that you are taking this medicine.

Taking Tamitect with food and drink
Take Tamitect on an empty stomach or 2 to 3 hours after a meal. Wait at least 1 hour until the next meal. Avoid grapefruit (also as juice) while on treatment with Tamitect since it can affect its levels.

Pregnancy and breast-feeding
If you are, think you might be or are planning to become pregnant, ask your doctor or pharmacist for advice before taking any medicine.

Tacrolimus passes into breast milk. Therefore you should not breast-feed whilst using Tamitect.

Driving and using machines
Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking this medicine. These effects are more frequently observed if you also drink alcohol.

Important information about some of the ingredients of Tamitect
Tamitect contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE TAMICTE
Always take Tamitect exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine.

This medicine should be taken twice a day. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight.

Initial doses just after transplantation will generally be in the range of 0.075 – 0.30 mg per kg body weight per day depending on the transplanted organ.

Your dose depends on your general condition and on which other immunosuppressive medication you are taking. Regular blood tests by your doctor will be required to define the correct dose and to adjust the dose from time to time. Your doctor will usually reduce your tacrolimus capsules dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take and how often.

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

If you take more Tamitect than you should
If you have accidentally taken too much see your doctor or contact your nearest hospital emergency department immediately.

If you forget to take Tamitect
Do not take a double dose to make up for forgotten individual doses.

If you have forgotten to take your capsules, wait until it is time for the next dose, and then continue as before.

If you stop taking Tamitect
Stopping your treatment may increase the risk of rejection of your transplanted organ. Do not stop your treatment unless your doctor tells you to do so.

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

4. POSSIBLE SIDE EFFECTS
Like all medicines, Tamitect can cause side effects, although not everybody gets them.

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

Severe effects may occur, including allergic and anaphylactic reactions. Benign and malignant tumours have been reported following treatment as a result of immunosuppression.

Possible side effects are listed according to the following categories:
Very common side effects are experienced in more than one in ten patients.
Common side effects are experienced in less than one in ten patients but in more than one per one hundred patients.
Uncommon side effects are experienced in less than one in one hundred patients but more than one per one thousand patients.
Rare side effects are experienced in less than one per one thousand patients but more than one per ten thousand patients.
Very rare side effects are experienced in less than one per ten thousand patients.
Very common side effects
- increased blood sugar, diabetes mellitus, increased potassium in the blood
- difficulty in sleeping
- trembling, headache
- increased blood pressure
- diarrhoea, nausea
- kidney problems

Common side effects
- reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts
- reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts (seen in blood tests)
- anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- blurred vision, increased sensitivity to light, eye disorders
- ringing sound in your ears
- reduced blood flow in the heart vessels, faster heartbeat
- bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- shortness in breath, changes in the lung tissue, collection of liquid around the lung, inflammation of the throat, cough, flu-like symptoms
- inflammations or ulcers causing abdominal pain or diarrhoea, bleedings in the stomach, inflammations or ulcers in the mouth, collection of fluid in the belly, vomiting, abdominal pains, indigestion, constipation, passing wind, bloating, loose stools, stomach problems
- changes in liver enzymes and function, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- itching, rash, hair loss, acne, increased sweating
- pain in joints, limbs or back, muscle cramps
- insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- general weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling feverish
- insufficient function of your transplanted organ

Uncommon side effects
- changes in blood clotting, reduction in the number of all types of blood cells
- dehydration, reduced protein or sugar in the blood, increased phosphate in the blood.
- coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- clouding of the eyes
- impaired hearing
- irregular heartbeat, skipped heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal EGG, heart rate and pulse abnormal
- blood clot in a vein of a limb, shock
- difficulties in breathing, respiratory tract disorders, asthma
- obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
- dermatitis, burning sensation in the sunlight
- joint disorders
- inability to urinate, painful menstruation and abnormal menstrual bleedings
- failure of some organs, influenza like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, increase of the enzyme lactate dehydrogenase in your blood, weight loss

Rare side effects
- small bleedings in your skin due to blood clots
- increased muscle stiffness
- blindness
- deafness
- collection of fluid around the heart
- acute breathlessness
- cyst formation in your pancreas
- problems with blood flow in the liver
- serious illness with blistering of skin, mouth, eyes and genitals, increased hairiness
- thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer
Very rare side effects
- muscular weakness
- abnormal heart scan
- liver failure, narrowing of the bile vessel
- painful urination with blood in the urine
- increase of fat tissue

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TAMITECT
- Keep out of the reach and sight of children.
- Store below 30°C
- Store in the original package (within the foil pouch) in order to protect from moisture & light.
- Do not use Tamitect after the expiry date which is stated on the carton and blister after {EXP}. Once the foil pouch is opened, the product should be used within 1 year. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Tamitect contains
Tamitsect 1 mg hard capsules
The active substance is tacrolimus.
For 1 mg: Each capsule contains 1 mg of tacrolimus
The other ingredients are:
- Capsule content: Povidone K-30, Croscarmellose Sodium (E 468), Lactose anhydrous, Magnesium stearate.
- Capsule shell: Titanium dioxide (E-171), Gelatin

What Tamitect looks like and contents of the pack
Tamitsect 1 mg hard capsules
White cap and white body hard shell capsules with white powder.
Tamitsect 1 mg hard capsules are supplied as blister strips containing 10 capsules within a protective foil wrapper, including a desiccant protecting the capsules from moisture. The desiccant should not be swallowed.
Tamitsect is available in blister packs containing blister strips of 10 capsules each.
7, 10, 14, 20, 28, 30, 50, 60, 100 capsules.

Marketing Authorization Holder
PharOS – Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Salaminas str.
15351 Pallini-Attikis
Greece

Manufacturer
Laboratorios Cifra, S.A.
Olaz-Chipi, 10-Pelay Areta 31620 Huarte-Pamplona, Navarra, Spain

mibe GmbH Arzneimittel
Münchner Strale 15, 08796 Brehna, Germany

SUN-FARM Sp. z o.o.
Częstochowa 75, 05-340 Kołbied, Poland

<This medicinal product is authorized in the Member States of the EEA under the following names :>
UK: Tamitsect 1mg hard capsules
AT: Tacrotect 1mg Hartkapseln
DE: Tacrotect 1mg Hartkapseln
PL: Tacrotec 1mg Kapsulka, twarda

This leaflet was last approved in 11/2011
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Tamitect is and what it is used for
2. Before you take Tamitect
3. How to take Tamitect
4. Possible side effects
5. How to store Tamitect
6. Further information

1. WHAT TAMICTECT IS AND WHAT IT IS USED FOR
Tamitect is an immunosuppressant. Following your organ transplant (e.g. liver, kidney, heart), your body's immune system will try to reject the new organ. Tamitect is used to control your body's immune response enabling your body to accept the transplanted organ.
Tamitect is often used in combination with other medicines that also suppress the immune system.
You may also be given Tamitect for an ongoing rejection of your transplanted liver, kidney, heart or other organ when any previous treatment you were taking was unable to control this immune response after your transplantation.

2. BEFORE YOU TAKE TAMICTECT
Do not take Tamitect
- If you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Tamitect. (See section 6)
- If you are allergic (hypersensitive) to sirolimus or to any macrolide antibiotic (e.g. erythromycin, clarithromycin, josamycin).

Take special care with Tamitect
Tell your doctor if any of the following apply to you:
- If you are taking any medicines mentioned below under 'Using other medicines'.
- If you have or have had liver problems
- If you have diarrhea for more than one day
- If you need to receive any vaccinations

Your doctor may need to adjust your dose of Tamitect.
You should keep in regular contact with your doctor. From time to time, your doctor may need to do blood, urine, heart, eye tests, to set the right dose of Tamitect.
You should limit your exposure to the sun and UV (ultraviolet) light whilst taking Tamitect. This is because immunosuppressants could increase the risk of skin cancer. Wear appropriate protective clothing and use a sunscreen with a high sun protection factor.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal preparations. Tamitect must not be taken with cyclosporine.
Tamitect blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Tamitect which may require an increase or decrease in dose. In particular, you should tell your doctor if you are taking or have recently taken medicines like:

- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections, such as ketoconazole, fluconazole, itraconazole, voriconazole, clindamycin, erythromycin, clarithromycin, josamycin, and rifampicin
- HIV medicines (e.g. ritonavir), used to treat HIV infection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazol or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- cisapride or the articular magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill or other hormone treatments with ethinyloestradiol, hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g. nifedipine, nicardipine, diltiazem and verapamil)
- medicines known as "statins" used to treat elevated cholesterol and triglycerides
- phenytoin or phenobarbital, used to treat epilepsy
- the corticosteroids prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression
- Herbal preparations containing St. John’s Wort (Hypericum perforatum)
Tell your doctor if you are taking or need to take ibuprofen, amphotericin B or antivirals (e.g. aciclovir). These may worsen kidney or nervous system problems when taken together with Tamitect.
Your doctor also needs to know if you are taking potassium supplements or certain diuretics used for heart failure, hypertension and kidney disease, (e.g. amiloride, triamterene, or spironolactone), non-steroidal anti-inflammatory drugs (NSAIDs; e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes, while you take Tamitect.
If you need vaccinations, tell your doctor in advance that you are taking this medicine.

Taking Tamitect with food and drink
Take Tamitect on an empty stomach or 2 to 3 hours after a meal. Wait at least 1 hour until the next meal. Avoid grapefruit (also as juice) while on treatment with Tamitect since it can affect its levels.

Pregnancy and breast-feeding
If you are, think you might be or are planning to become pregnant, ask your doctor or pharmacist for advice before taking any medicine.
Tacrolimus passes into breast milk. Therefore you should not breast-feed whilst using Tamitect.

Driving and using machines
Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking this medicine. These effects are more frequently observed if you also drink alcohol.

Important information about some of the ingredients of Tamitect
Tamitect contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE TAMICTECT
Always take Tamitect exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine.
This medicine should be taken twice a day. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.
The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial doses just after transplantation will generally be in the range of 0.075 – 0.30 mg per kg body weight per day depending on the transplanted organ.
Your dose depends on your general condition and on which other immunosuppressive medication you are taking. Regular blood tests by your doctor will be required to define the correct dose and to adjust the dose from time to time. Your doctor will usually reduce your tacrolimus capsules dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take and how often.
Tacrolimus is taken orally twice daily, usually in the morning and evening. You should generally take Tacrolimus capsules on an empty stomach or at least 1 hour before or 2 to 3 hours after the meal. The capsules should be swallowed whole with a glass of water. Avoid grapefruit and grapefruit juice while taking Tacrolimus capsules. Do not swallow the desiccant contained in the foil wrapper.

If you take more Tamitect than you should
If you have accidentally taken too much see your doctor or contact your nearest hospital emergency department immediately.

If you forget to take Tamitect
Do not take a double dose to make up for forgotten individual doses.
If you have forgotten to take your capsules, wait until it is time for the next dose, and then continue as before.

If you stop taking Tamitect
Stopping your treatment may increase the risk of rejection of your transplanted organ. Do not stop your treatment unless your doctor tells you to do so.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Tamitect can cause side effects, although not everybody gets them.
Tamitect reduces your body's own defence mechanism to stop you rejecting your transplanted organ. Consequently, your body will not be as good as usual at fighting infections. So if you are taking Tamitect you may therefore catch more infections than usual such as infections of the skin, mouth, stomach and intestines, lungs and urinary tract.
Severe effects may occur, including allergic and anaphylactic reactions. Benign and malignant tumours have been reported following treatment as a result of immunosuppression.

Possible side effects are listed according to the following categories:
Very common side effects are experienced in more than one in ten patients.
Common side effects are experienced in less than one in ten patients but in more than one per one hundred patients.
Uncommon side effects are experienced in less than one in one hundred patients but more than one per one thousand patients.
Rare side effects are experienced in less than one per one thousand patients but more than one per ten thousand patients.
Very rare side effects are experienced in less than one per ten thousand patients.
### Very common side effects
- increased blood sugar, diabetes mellitus, increased potassium in the blood
- difficulty in sleeping
- trembling, headache
- increased blood pressure
- diarrhoea, nausea
- kidney problems

### Common side effects
- reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts
- reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts (seen in blood tests)
- anxiety symptoms, confusion and disorientation, depression, mood changes, nightmares, hallucination, mental disorders
- fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- blurred vision, increased sensitivity to light, eye disorders
- ringing sound in your ears
- reduced blood flow in the heart vessels, faster heartbeat
- bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- shortness in breath, changes in the lung tissue, collection of fluid around the lung, inflammation of the throat, cough, flu-like symptoms
- inflammations or ulcers causing abdominal pain or diarrhoea, bleedings in the stomach, inflammations or ulcers in the mouth, collection of fluid in the belly, vomiting, abdominal pains, indigestion, constipation, passing wind, bloating, loose stools, stomach problems
- changes in liver enzymes and function, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- itching, rash, hair loss, acne, increased sweating
- pain in joints, limbs or back, muscle cramps
- insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- general weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling feverish
- insufficient function of your transplanted organ

### Uncommon side effects
- changes in blood clotting, reduction in the number of all types of blood cells
- dehydration, reduced protein or sugar in the blood, increased phosphate in the blood.
- coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- clouding of the eyes
- impaired hearing
- irregular heartbeat, skipped heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
- blood clot in a vein of a limb, shock
- difficulties in breathing, respiratory tract disorders, asthma
- obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
- dermatitis, burning sensation in the sunlight
- joint disorders
- inability to urinate, painful menstruation and abnormal menstrual bleedings
- failure of some organs, influenza like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, increase of the enzyme lactate dehydrogenase in your blood, weight loss

### Rare side effects
- small bleedings in your skin due to blood clots
- increased muscle stiffness
- blindness
- deafness
- collection of fluid around the heart
- acute breathlessness
- cyst formation in your pancreas
- problems with blood flow in the liver
- serious illness with blistering of skin, mouth, eyes and genitals, increased hairiness
- thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer
Very rare side effects
- muscular weakness
- abnormal heart scan
- liver failure, narrowing of the bile vessel
- painful urination with blood in the urine
- increase of fat tissue

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TAMICTECT
- Keep out of the reach and sight of children.
- Store below 30°C
- Store in the original package (within the foil pouch) in order to protect from moisture & light.
- Do not use Tamictect after the expiry date which is stated on the carton and blister after {EXP}. Once the foil pouch is opened, the product should be used within 1 year. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Tamictect contains
Tamictect 5 mg hard capsules
The active substance is tacrolimus.
For 5 mg: Each capsule contains 5mg of tacrolimus
The other ingredients are:
- Capsule content: Povidone K-30, Croscarmellose Sodium (E 468), Lactose anhydrous, Magnesium stearate.
- Capsule shell: Titanium dioxide (E-171), Gelatin

What Tamictect looks like and contents of the pack
Tamictect 5 mg hard capsules
White cap and white body hard shell capsules with white powder.
Tamictect 5 mg hard capsules are supplied as blister strips containing 10 capsules within a protective foil wrapper, including a desiccant protecting the capsules from moisture. The desiccant should not be swallowed.
Tamictect is available in blister packs containing blister strips of 10 capsules each.
7, 10, 14, 20, 28, 30, 50, 60, 100 capsules.

Marketing Authorization Holder
PharOS – Pharmaceutical Oriented Services Ltd
87, Marathoonos Ave & Salaminas str.
15351 Pallini-Attikis
Greece

Manufacturer
Laboratorios Cinfa, S.A.
Olaz-Chipi, 10-Polvg Areta 31620 Huarte-Pamplona, Navarra, Spain

mbbe GmbH Arzneimittel
Münchener Strale 15, 06796 Brehna, Germany

SUN-FARM Sp. z o.o.
Czętkowi 73, 06-340 Kobiel, Poland

<This medicinal product is authorized in the Member States of the EEA under the following names :>
UK: Tamictect 5mg hard capsules
AT: Tacrolet 5mg Hartkapseln
DE: Tacrolet 5mg Hartkapseln
PL: Tacrolet 5mg Kapsułka, twarda

This leaflet was last approved in 11/2011
Module 4
Labelling

Please note that there are no mock-ups available for PL 23022/0091-3, therefore the labelling shown is the labelling for PL 23022/0094-6 only. The marketing authorisation holder has stated that it does not intend to market the products for PL 23022/0091-3 and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling mock-ups for PL 23022/0091-3 for review to the regulatory authority before marketing the products.
Tamitect
0.5 mg hard capsules
Tacrolimus
As directed by your doctor
PL 23022/0094

Each Tamitect 0.5 mg hard capsule contains 0.5 mg tacrolimus. 0.5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard. Oral use. Read the package leaflet before use.
Keep out of the reach and sight of children. Do not swallow the desiccant.
This medicine should be taken twice daily.
Store below 30°C. Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

Tamitect 0.5 mg hard capsules
As directed by your doctor

TAMITECT 0.5 mg, hard capsules
Tacrolimus
EXP:
LOT:
50 hard capsules
Oral use
The pouch contains desiccant
Do not swallow

PharoS
Pharmaceutical Oriented Services Ltd
87, Marathonom Ave & Salaminis str.,
15351 Pallini-Attika, Greece

POM

0.5mg - PL 23022/0094
Tamitect 0.5 mg hard capsules
Tacrolimus

As directed by your doctor

Each Tamitect 0.5 mg hard capsule contains 0.5 mg tacrolimus. 0.5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard. Oral use. Read the package leaflet before use.

Keep out of the reach and sight of children.
Do not swallow the desiccant. This medicine should be taken twice daily.
Store below 30°C.
Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

POM
PharOSS
Pharmaceutical Oriented Services Ltd
87, Marathonom Ave & Sarantinos str,
15351 Pallino-Attika, Greece

TAMITEC 0.5 mg, hard capsules
Tacrolimus
EXP:
LOT:
30 hard capsules

Oral use
The pouch contains desiccant
Do not swallow

PharoS
0.5mg - PL 23022/0094
Tamitect
0.5 mg hard capsules
Tacrolimus

As directed by your doctor

PL 23022/0094

Each Tamitect 0.5 mg hard capsule contains 0.5 mg tacrolimus. 0.5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsules, hard, Oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not swallow the desiccant. This medicine should be taken twice daily. Store below 30°C. Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

PharOS
Pharmaceutical Oriented Services Ltd
97, Marathonom AVE & Salaminos str,
15351 Pollini-Attikis, Greece

TAMITECT 0.5 mg, hard capsules
Tacrolimus
EXP:
LOT:
20 hard capsules
Oral use
The pouch contains desiccant
Do not swallow

PharOS
0.5mg - PL 23022/0094
Tamitect
1 mg hard capsules
Tacrolimus
30 hard capsules
Oral use

As directed by your doctor

Each Tamitect 1 mg hard capsule contains 1 mg tacrolimus. 1 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard. Oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not swallow the desiccant. This medicine should be taken twice daily.

Store below 30°C. Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

Affix dispensing label here

PharOS
Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Galanias str.
15351 Pallini-Attika, Greece

TAMITECT 1 mg, hard capsules
Tacrolimus
EXP:
LOT:
30 hard capsules

Oral use
The pouch contains desiccant
Do not swallow

PharOS
1mg - PL23022/0095
Tamitect
1 mg hard capsules
Tacrolimus

28 hard capsules
Oral use

Each Tamitect 1 mg hard capsule contains 1 mg tacrolimus. 1 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard. Oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not swallow the desiccant. This medicine should be taken twice daily. Store below 30°C. Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

PharOS
Pharmaceutical Oriented Services Ltd
87, Marathoros Ave & Salaminias str,
15361 Pallini-Attilia, Greece

POM

TAMITECT 1 mg, hard capsules
Tacrolimus
EXP:
LOT:
28 hard capsules

Oral use
The pouch contains desiccant
Do not swallow

PharOS
1 mg - PL23022/0095
Tamitect
1 mg hard capsules
Tacrolimus

As directed by your doctor

Each Tamitect 1 mg hard capsule contains 1 mg tacrolimus. 1 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard, Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Do not swallow the desiccant. This medicine should be taken twice daily. Store below 30°C.

Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

PharmOEL
Pharmaceutical Oriented Services Ltd
87, Marathanos Ave & Salaminias str.
15561 Pallini-Athens, Greece

TAMITEC 1 mg, hard capsules
Tacrolimus
EXP:
LOT:
20 hard capsules

Oral use
The pouch contains desiccant
Do not swallow

PharoS
1mg - PL23022/0095
PAR Miloprosan/Tamitect 0.5 mg Hard Capsules
Miloprosan/Tamitect 1 mg Hard Capsules
Miloprosan/Tamitect 5 mg Hard Capsules

Tamitect
1 mg hard capsules
Tacrolimus

14 hard capsules
Oral use

Tamitect 1 mg hard capsules
Tacrolimus
As directed by your doctor
PL 23022/0095

Each Tamitect 1 mg hard capsule contains 1 mg tacrolimus.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not swallow the desiccant. This medicine should be taken twice daily. Store below 30°C.
Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

Affix dispensing label here

PharoS
Pharmaceutical Oriented Services Ltd
87, Marathonom Ave & Salaminas str.
15351 Paliini-Attikis, Greece

TAMITECT 1 mg, hard capsules
Tacrolimus
EXP:
LOT:
14 hard capsules

Oral use
The pouch contains desiccant
Do not swallow

PharoS
1mg - PL23022/0095
TAMITECT 1 mg, hard capsules
Tacrolimus

EXP:
LOT:
60 hard capsules

Oral use
The pouch contains desiccant
Do not swallow
Tamitect 5 mg hard capsules
Tacrolimus
As directed by your doctor
PL 23022/0096

Each Tamitect 5 mg hard capsule contains 5 mg tacrolimus.
5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard, Oral use. Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not swallow the desiccant. This medicine should be taken twice daily. Store below 30°C.
Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

PharoS
Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Salaminas str.
15351 Pallini-Attikis, Greece

TAMITEC 5 mg, hard capsules
Tacrolimus
EXP:
LOT:
7 hard capsules
Oral use
The pouch contains desiccant
Do not swallow
PharoS
5mg - PL 23022/0096
Tamitect 5 mg hard capsules
Tacrolimus

As directed by your doctor

PL 23022/0096

Each Tamitect 5 mg hard capsule contains 5 mg tacrolimus. 5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard. Oral use. Read the package leaflet before use.

Keep out of the reach and sight of children. Do not swallow the desiccant. This medicine should be taken twice daily.

Store below 30°C. Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

PharoS
Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Salaminias str,
13351 Pallini, Athens, Greece

TAMITECT 5 mg, hard capsules
Tacrolimus

EXP:
LOT:
50 hard capsules

Oral use
The pouch contains desiccant
Do not swallow

PharoS
5mg - PL 23022/0096
Tamitect
5 mg hard capsules
Tacrolimus
30 hard capsules
Oral use

Each Tamitect 5 mg hard capsule contains 5 mg tacrolimus. 5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule hard. Oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not swallow the desiccant. This medicine should be taken twice daily. Store below 30°C. Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

PharOS
Pharmaceutical Oriented Services Ltd
87, Monathosos Ave & Solammos str.
15351 Pallini-Athens, Greece

TAMITECT 5 mg, hard capsules
Tacrolimus
EXP:
LOT:
30 hard capsules

Oral use
The pouch contains desiccant
Do not swallow

PharOS
5mg - PL 23022/0096
Tamitect 5 mg hard capsules
Tacrolimus
As directed by your doctor
PL 23022/0096

Each Tamitect 5 mg hard capsule contains 5 mg tacrolimus. 5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard. Oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not swallow the desiccant.

This medicine should be taken twice daily.
Store below 30°C.
Store in the original package (within the foil pouch) in order to protect from light & moisture.
Medicinal product subject to medical prescription.

Affix dispensing label here

PharoS
Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Sotirouminis str.
15351 Panni-Anthisi, Greece

TAMITECT 5 mg, hard capsules
Tacrolimus
EXP:
LOT:
28 hard capsules

Oral use
The pouch contains desiccant
Do not swallow

PharoS
5mg - PL 23022/0096
Tamitect
5 mg hard capsules
Tacrolimus
20 hard capsules
Oral use

Each Tamitect 5 mg hard capsule contains 5 mg tacrolimus. 5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard. Oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not swallow the desiccant. This medicine should be taken twice daily. Store below 30°C. Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

PharOS
Pharmaceutical Oriented Services Ltd
87, Marathonos Ave & Salaminas str.
15351 Pallini-Attica, Greece

TAMITECT 5 mg, hard capsules
Tacrolimus
EXP:
LOT:
20 hard capsules
Oral use
The pouch contains desiccant
Do not swallow

PharOS
5mg - PL 23022/0096
Tamitect 5 mg hard capsules
Tacrolimus

14 hard capsules
Oral use

Each Tamitect 5 mg hard capsule contains 5 mg tacrolimus. 5 mg: Contains lactose anhydrous. See package leaflet for further information. Capsule, hard. Oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not swallow the desiccant. This medicine should be taken twice daily. Store below 30°C. Store in the original package (within the foil pouch) in order to protect from light & moisture. Medicinal product subject to medical prescription.

PharOS
Pharmaceutical Oriented Services Ltd
87, Marathones Ave & Salaminias str.
15351 Pallini-Attiko, Greece

TAMITECT 5 mg, hard capsules
Tacrolimus
EXP:
LOT:
14 hard capsules
Oral use
The pouch contains desiccant
Do not swallow

PharOS
5mg - PL 23022/0096
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the relevant member states considered that the applications for Miloprosan/Tamitect 0.5 mg, 1 mg and 5 mg hard capsules could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS) and the following as concerned member states (CMS):

- UK/H/4470/001-3/DC: Germany (DE), Denmark (DK), Finland (FI), the Netherlands (NL), Portugal (PT) and Sweden (SE).
- UK/H/4643/001-3/DC: Austria (AT), Germany (DE) and Poland (PL).

Miloprosan/Tamitect 0.5 mg, 1 mg and 5 mg hard capsules are prescription only medicines (POM) and are indicated for:

- Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
- Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

These applications for Miloprosan/Tamitect 0.5 mg, 1 mg and 5 mg hard capsules were submitted according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Prograf 0.5 mg, 1 mg and 5 mg Hartkapseln (hard capsules), first authorised in Germany to Astellas Pharma GmbH on 3rd June 1998.

The UK reference products are Prograf Hard Capsules 0.5 mg, 1 mg and 5 mg, first authorised to Fujisawa Limited on 15th September 1999 and 7th June 1994 (PL 13424/0004, 0001-2). These licences then underwent a change of ownership to Astellas Pharma Limited on 18th November 2005 and 16th November 2005 (PL 00166/0206, 0203-4).

Tacrolimus is a calcineurin inhibitor. It is derived from the fungus *Streptomyces tsukubaensis* and has a macrolide structure. Inhibition of calcineurin in T lymphocytes leads to calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of lymphokine genes. 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.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for these applications as the pharmacology of tacrolimus is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of Good Manufacturing Practice (GMP) are in place at those sites.
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan was provided. It concluded that routine risk minimisation activities were sufficient for the two main risks, medication errors, including errors during therapy regimen change. The Marketing Authorisation Holder (MAH) also committed to implement detailed and systematic follow-up of all individual case safety reports which involve medication errors.
## II. ABOUT THE PRODUCT

| Name of the products in the Reference Member State | Miloprosan 0.5 mg hard capsules  
| Miloprosan 1 mg hard capsules  
| Miloprosan 5 mg hard capsules  
| Tamitect 0.5 mg hard capsules  
| Tamitect 1 mg hard capsules  
| Tamitect 5 mg hard capsules |
| Name(s) of the active substance(s) (INN) | Tacrolimus |
| Pharmacotherapeutic classification (ATC code) | Calcineurin inhibitor  
| ATC Code: L04AD02 |
| Pharmaceutical form and strength(s) | 0.5 mg hard capsules  
| 1 mg hard capsules  
| 5 mg hard capsules |
| Reference numbers for the Decentralised Procedure | UK/H/4470/001/DC  
| UK/H/4470/002/DC  
| UK/H/4470/003/DC  
| UK/H/4643/001/DC  
| UK/H/4643/002/DC  
| UK/H/4643/003/DC |
| Reference Member State | United Kingdom (UK) |
| Member States concerned | UK/H/4470/001-3/DC: Germany (DE), Denmark (DK), Finland (FI), the Netherlands (NL), Portugal (PT) and Sweden (SE)  
| UK/H/4643/001-3/DC: Austria (AT), Germany (DE) and Poland (PL) |
| Marketing Authorisation Number(s) | PL 23022/0091  
| PL 23022/0092  
| PL 23022/0093  
| PL 23022/0094  
| PL 23022/0095  
| PL 23022/0096 |
| Name and address of the authorisation holder | PharOs-Pharmaceutical Oriented Services Ltd  
| 87, Marathonos Ave & Salaminas Str.  
| 15351 Pallini Attikis  
| Greece |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN name: Tacrolimus

Chemical name: (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-Hexadecahydro-5,19-dihydroxy-3-\{[(1E)-2 \[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl\]-1-methylethenyl\]-14,16-dimethoxy 4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1c][1,4]oxazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate, 17-allyl-1,14 dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone, monohydrate

Structure:

Physical form: A white to off-white, crystalline powder.

Solubility: Soluble in methanol, ethanol, ethyl acetate, acetone, chloroform, diethyl ether, sparingly soluble in hexane, petroleum ether, insoluble in water.

Molecular formula: C_{44}H_{69}NO_{12} • H_{2}O

Molecular weight: 822

Tacrolimus complies with in-house specifications.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines.

Stability studies have been performed with the active substance and no significant changes were observed. On the basis of the results, a suitable re-test period could be approved.
P. Medicinal Product

Other Ingredients
Other ingredients in the capsule consist of pharmaceutical excipients povidone K-30, croscarmellose sodium (E468), lactose anhydrous and magnesium stearate.

The ingredients in the capsule shell are titanium dioxide (E171) and gelatin. The 0.5 mg capsules have the extra excipient yellow iron oxide (E172). The 5 mg capsules have the extra excipient red iron oxide (E-172).

All excipients comply with their respective European Pharmacopoeia monographs.

With the exception of lactose anhydrous, none of the excipients used contain material of animal or human origin. The suppliers of the excipients have provided declarations that neither the excipients nor any material used in the production of the excipients pose a TSE risk. Confirmation has been provided that the magnesium stearate used is of vegetable origin. The applicant has provided a declaration that the milk used in the production of anhydrous lactose is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products containing tacrolimus that could be considered generic medicinal products of Prograf 0.5 mg, 1 mg and 5 mg hard capsules authorised in Ireland to Fujisawa Ireland Limited, on 16th February 1996. The 5 mg strength capsules were also used as the reference product in the bioequivalence study. These products are considered to be pharmaceutically equivalent to the UK reference products.

The applicant has provided suitable product development sections. Valid justification for the use and amounts of each excipient has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and reference products.

Manufacturing Process
A satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches of all strengths have been provided and are satisfactory.

The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification
The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.
Container-Closure System
These products are packaged in blisters composed of polyvinyl chloride (PVC), polyvinylidene chloride (PVdC) and aluminium. The blisters are then placed with dessicant in an aluminium foil sachet.

Pack sizes are:
Miloprosan 0.5 mg hard capsules (PL 23022/0091): 20, 30, 50 and 100 capsules.
Miloprosan 1 mg hard capsules (PL 23022/0092): 20, 50, 60 and 100 capsules.
Miloprosan 5 mg hard capsules (PL 23022/0093): 30, 50, 60, 100 capsules.

Tamitect 0.5 mg hard capsules (PL 23022/0094): 7, 10, 14, 20, 28, 30, 50, 60, 100 capsules.
Tamitect 1 mg hard capsules (PL 23022/0095): 7, 10, 14, 20, 28, 30, 50, 60, 100 capsules.
Tamitect 5 mg hard capsules (PL 23022/0096): 7, 10, 14, 20, 28, 30, 50, 60, 100 capsules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU Directive 2002/72/EC for contact with food.

Stability of the Product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with the storage instructions ‘Store below 30°C, in the original package, to protect from moisture & light’.
The shelf-life of the product after opening the aluminium foil sachet is 1 year. This is satisfactory.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling
The SmPCs, PILs and labelling are pharmaceutically acceptable. The UK approved SmPCs, PILs and label mock-ups are included in modules 2, 3 and 4 of this report.

User testing results of a similar PIL for already approved products, Evenil/Taliximum/Tacrolimus/Takon/Aletris/Tacni 0.5 mg, 1 mg and 5 mg hard capsules (PL 23022/0012-20, 0062-70, 0078-80; UK/H/2177, 2178, 2179, 3027, 3028, 3029, 3100/001-3/DC) have been submitted with a satisfactory bridging report. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that the leaflet contains.

MAA (Marketing Authorisation Application) Forms
The MAA forms are pharmaceutically satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of tacrolimus are well-known. As tacrolimus is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature is therefore appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Satisfactory justification for the absence of an Environmental Risk Assessment was provided.

From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3 CLINICAL ASPECTS

Clinical Pharmacology

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

Bioequivalence study

An randomised, single dose, two treatment, two period, open label crossover study to compare the pharmacokinetics of the test product Miloprosan/Tamitect 5 mg hard capsules versus the reference product Prograf (tacrolimus) 5 mg hard capsules (Fujisawa Ireland Limited, Ireland) in healthy subjects under fasted conditions.

Blood samples were taken at baseline and up to 168 hours post dose. There was a washout period of 25 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tacrolimus are presented below as non-transformed values for geometric means:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0\rightarrow t} (ng/ml/h)</th>
<th>AUC_{0\rightarrow \infty} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
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<tr>
<td>Test (T)</td>
<td>260.236 ± 149.617</td>
<td>279.685 ± 155.996</td>
<td>32.534 ± 11.509</td>
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<tr>
<td>Reference (R)</td>
<td>261.606 ± 160.329</td>
<td>281.575 ± 171.173</td>
<td>32.526 ± 11.293</td>
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<tr>
<td>*T/R Ratio (90 % CI)</td>
<td>98.728 (93.06 – 104.74)</td>
<td>99.009 (93.61 – 104.72)</td>
<td>111.574</td>
</tr>
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</table>

AUC_{0\rightarrow t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0\rightarrow \infty} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
* log-transformed values

The Efficacy Working Party (EWP) therapeutic sub group on Pharmacokinetics recommends that the bioequivalence acceptance criteria for tacrolimus should be tightened to 90.00-111.00 % for AUC and remain at 80.00-125.00 % for C_{max} (EMA/618604/2008 Rev 3). The results for the primary variables indicated that the 90 % confidence intervals test/reference ratio of geometric means for AUC_{0\rightarrow t} and C_{max} for tacrolimus lie within acceptable limits. Thus, bioequivalence has been shown between the test and reference products in this study.

As the product range meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) for a biowaiver for the other strengths, the results and conclusions of the bioequivalence study on the 5 mg strength can be extrapolated to Miloprosan/Tamitect 0.5 mg and 1 mg hard capsules.

Efficacy

No new efficacy data were submitted with these generic applications and none were required.
Safety
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns arose during the bioequivalence study.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling
The SmPCs, PILs and labelling are clinically satisfactory and consistent with those for the reference products.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Forms
The MAA forms are clinically satisfactory.

Conclusions
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Miloprosan/Tamitect 0.5 mg, 1 mg and 5 mg hard capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Miloprosan/Tamitect 5 mg hard capsules and the reference product Prograf 5 mg hard capsules. A biowaiver is accepted and justified for Miloprosan/Tamitect 0.5 mg and 1 mg hard capsules.

No new or unexpected safety concerns arose from the bioequivalence study.

The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tacrolimus is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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