ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCT, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Astellas Pharma Ges.m.b.H. Linzerstraße 221 – 227 1140 Vienna Austria	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Austria	Astellas Pharma Ges.m.b.H. Linzerstraße 221 – 227 1140 Vienna Austria	Prograf	0.5 mg	Hard Capsules	Oral use
Austria	Astellas Pharma Ges.m.b.H. Linzerstraße 221 – 227 1140 Vienna Austria	Prograf	1 mg	Hard Capsules	Oral use
Austria	Astellas Pharma Ges.m.b.H. Linzerstraße 221 – 227 1140 Vienna Austria	Prograf	5 mg	Hard Capsules	Oral use
Belgium	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograft	0.5 mg	Hard Capsules	Oral use
Belgium	Fujisawa GmbH Neumarkter Str. 61 81673 München Germany	Prograft	1 mg	Hard Capsules	Oral use
Belgium	Fujisawa GmbH Neumarkter Str. 61 81673 München Germany	Prograft	5 mg	Hard Capsules	Oral use
Belgium	Fujisawa GmbH Neumarkter Str. 61 81673 München Germany	Prograft	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use

Cyprus	Medilink Pharmaceuticals Ltd. 30 Armenias P.O. Box 25676 2003 Strovolos 1640 Nicosia	Prograf	1 mg	Hard Capsules	Oral use
Cyprus	Medilink Pharmaceuticals Ltd. 30 Armenias P.O. Box 25676 2003 Strovolos 1640 Nicosia	Prograf	5 mg	Hard Capsules	Oral use
Cyprus	Medilink Pharmaceuticals Ltd. 30 Armenias P.O. Box 25676 2003 Strovolos 1640 Nicosia	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Czech Republic	Astellas Pharma s.r.o. Meteor Office Centre Park Sokolovská 100/94 186 00 Praha 8 Czech Republic	Prograf	0.5 mg	Hard Capsules	Oral use
Czech Republic	Astellas Pharma s.r.o. Meteor Office Centre Park Sokolovská 100/94 186 00 Praha 8 Czech Republic	Prograf	1 mg	Hard Capsules	Oral use
Czech Republic	Astellas Pharma s.r.o. Meteor Office Centre Park Sokolovská 100/94 186 00 Praha 8 Czech Republic	Prograf	5 mg	Hard Capsules	Oral use
Czech Republic	Astellas Pharma s.r.o. Meteor Office Centre Park Sokolovská 100/94 186 00 Praha 8 Czech Republic	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use

Germany	Astellas Pharma GmbH Neumarkter Str. 61 81673 München Germany	Prograf	0.5 mg	Hard Capsules	Oral use
Germany	Astellas Pharma GmbH Neumarkter Str. 61 81673 München Germany	Prograf	1 mg	Hard Capsules	Oral use
Germany	Astellas Pharma GmbH Neumarkter Str. 61 81673 München Germany	Prograf	5 mg	Hard Capsules	Oral use
Germany	Astellas Pharma GmbH Neumarkter Str. 61 81673 München Germany	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Denmark	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	0.5 mg	Hard Capsules	Oral use
Denmark	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	1 mg	Hard Capsules	Oral use
Denmark	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	5 mg	Hard Capsules	Oral use
Denmark	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Greece	Vianex S.A. Tatoiou Street Lamia National Road 14671 Nea Erythrea Greece	Prograf	0.5 mg	Hard Capsules	Oral use

Greece	Vianex S.A. Tatoiou Street Lamia NationalRoad 14671 Nea Erythrea Greece	Prograf	1 mg	Hard Capsules	Oral use
Greece	Vianex S.A. Tatoiou Street Lamia NationalRoad 14671 Nea Erythrea Greece	Prograf	5 mg	Hard Capsules	Oral use
Greece	Vianex S.A. Tatoiou Street Lamia NationalRoad 14671 Nea Erythrea Greece	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Spain	Astellas Pharma S.A Paseo del Club Deportivo n°1, Bloque 14 28223 Pozuelo de Alarcón (Madrid) Spain	Prograf	0,5 mg	Hard Capsules	Oral use
Spain	Astellas Pharma S.A Paseo del Club Deportivo n°1, Bloque 14 28223 Pozuelo de Alarcón (Madrid) Spain	Prograf	1 mg	Hard Capsules	Oral use
Spain	Astellas Pharma S.A Paseo del Club Deportivo n°1, Bloque 14 28223 Pozuelo de Alarcón (Madrid) Spain	Prograf	5 mg	Hard Capsules	Oral use
Spain	Astellas Pharma S.A Paseo del Club Deportivo n°1, Bloque 14 28223 Pozuelo de Alarcón (Madrid) Spain	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use

Finland	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	0.5 mg	Hard Capsules	Oral use
Finland	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	1 mg	Hard Capsules	Oral use
Finland	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	5 mg	Hard Capsules	Oral use
Finland	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
France	Astellas Pharma S.A.S. 114 rue Victor Hugo 92300 Levallois Perret France	Prograf	0.5 mg	Hard Capsules	Oral use
France	Astellas Pharma S.A.S. 114 rue Victor Hugo 92300 Levallois Perret France	Prograf	1 mg	Hard Capsules	Oral use
France	Astellas Pharma S.A.S. 114 rue Victor Hugo 92300 Levallois Perret France	Prograf	5 mg	Hard Capsules	Oral use
France	Astellas Pharma S.A.S. 114 rue Victor Hugo 92300 Levallois Perret France	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Hungary	Fujisawa GmbH** Neumarkter Str. 61 81673 München Germany	Prograf	0.5 mg	Hard Capsules	Oral use

Hungary	Fujisawa GmbH** Neumarkter Str. 61 81673 München Germany	Prograf	1 mg	Hard Capsules	Oral use
Hungary	Fujisawa GmbH** Neumarkter Str. 61 81673 München Germany	Prograf	5 mg	Hard Capsules	Oral use
Hungary	Fujisawa GmbH** Neumarkter Str. 61 81673 München Germany	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Ireland	Astellas Pharma Co. Ltd. 25, The Courtyard Kilcarbery Business Park Clondalkin, Dublin 22 Ireland	Prograf	0.5 mg	Hard Capsules	Oral use
Ireland	Astellas Pharma Co. Ltd. 25, The Courtyard Kilcarbery Business Park Clondalkin, Dublin 22 Ireland	Prograf	1 mg	Hard Capsules	Oral use
Ireland	Astellas Pharma Co. Ltd. 25, The Courtyard, Kilcarbery Business Park Clondalkin, Dublin 22 Ireland	Prograf	5 mg	Hard Capsules	Oral use
Ireland	Astellas Pharma Co. Ltd. 25, The Courtyard Kilcarbery Business Park Clondalkin, Dublin 22 Ireland	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Italy	Astellas Pharma S.p.A. Via delle Industrie 1 20061 Carugate (Milano) Italy	Prograf	0.5 mg	Hard Capsules	Oral use

Italy	Astellas Pharma S.p.A. Via delle Industrie 1 20061 Carugate (Milano) Italy	Prograf	1 mg	Hard Capsules	Oral use
Italy	Astellas Pharma S.p.A. Via delle Industrie 1 20061 Carugate (Milano) Italy	Prograf	5 mg	Hard Capsules	Oral use
Italy	Astellas Pharma S.p.A. Via delle Industrie 1 20061 Carugate (Milano) Italy	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Luxembourg	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograft	0.5 mg	Hard Capsules	Oral use
Luxembourg	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograft	1 mg	Hard Capsules	Oral use
Luxembourg	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograft	5 mg	Hard Capsules	Oral use
Luxembourg	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograft	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
The Netherlands	Astellas Pharma B.V. Postbus 108 2350 AC Leiderdorp The Netherlands	Prograft	0.5 mg	Hard Capsules	Oral use
The Netherlands	Astellas Pharma B.V. Postbus 108 2350 AC Leiderdorp The Netherlands	Prograft	1 mg	Hard Capsules	Oral use

The Netherlands	Astellas Pharma B.V. Postbus 108 2350 AC Leiderdorp The Netherlands	Prograft	5 mg	Hard Capsules	Oral use
The Netherlands	Astellas Pharma B.V. Postbus 108 2350 AC Leiderdorp The Netherlands	Prograft	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Norway	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	0.5 mg	Hard Capsules	Oral use
Norway	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	1 mg	Hard Capsules	Oral use
Norway	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf 5 mg Capsules	5 mg	Hard Capsules	Oral use
Norway	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Poland	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograf	0.5 mg	Hard Capsules	Oral use
Poland	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograf	1 mg	Hard Capsules	Oral use
Poland	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograf	5 mg	Hard Capsules	Oral use

Poland	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Portugal	Astellas Farma Limitada Edifício Cinema Rua José Fontana, n° 1, 1° andar 2770-101 Paço de Arcos Portugal	Prograf	0.5 mg	Hard Capsules	Oral use
Portugal	Astellas Farma Limitada Edifício Cinema Rua José Fontana, n° 1, 1° andar 2770-101 Paço de Arcos Portugal	Prograf	1 mg	Hard Capsules	Oral use
Portugal	Astellas Farma Limitada Edifício Cinema Rua José Fontana, n° 1, 1° andar 2770-101 Paço de Arcos Portugal	Prograf	5 mg	Hard Capsules	Oral use
Portugal	Astellas Farma Limitada Edifício Cinema Rua José Fontana, n° 1, 1° andar 2770-101 Paço de Arcos Portugal	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
Slovakia	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograf	1 mg	Hard Capsules	Oral use
Slovakia	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograf	5 mg	Hard Capsules	Oral use
Slovakia	Fujisawa GmbH* Neumarkter Str. 61 81673 München Germany	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use

Slovenia	Pharma Swiss d.o.o. Wolfova 1 1000 Ljubljana Slovenia	Prograf	1 mg	Hard Capsules	Oral use
Slovenia	Pharma Swiss d.o.o. Wolfova 1 1000 Ljubljana Slovenia	Prograf	5 mg	Hard Capsules	Oral use
Sweden	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	0.5 mg	Hard Capsules	Oral use
Sweden	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	1 mg	Hard Capsules	Oral use
Sweden	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	5 mg	Hard Capsules	Oral use
Sweden	Astellas Pharma a/s Naverland 4 2600 Glostrup Denmark	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use
United Kingdom	Astellas Pharma Ltd. Lovett House, Lovett Road Staines Middlesex TW18 3AZ United Kingdom	Prograf	0.5 mg	Hard Capsules	Oral use
United Kingdom	Astellas Pharma Ltd. Lovett House, Lovett Road Staines Middlesex TW18 3AZ United Kingdom	Prograf	1 mg	Hard Capsules	Oral use

United Kingdom	Astellas Pharma Ltd. Lovett House, Lovett Road Staines Middlesex TW18 3AZ United Kingdom	Prograf	5 mg	Hard Capsules	Oral use
United Kingdom	Astellas Pharma Ltd. Lovett House, Lovett Road Staines Middlesex TW18 3AZ United Kingdom	Prograf	5 mg/ml	Concentrate for Solution for Infusion	Intravenous use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY (IES) OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF PROGRAF / PROGRAFT HARD CAPSULES AND CONCENTRATE FOR INFUSION

Due to the fact that the original product Prograf and associated names does not have the same Summary of Product Characteristics (SPC) in the various Member States in the European Union and due to divergent national decisions, a harmonisation of the SPC for Prograf and associated names, throughout Europe became necessary.

Fujisawa GmbH acting on behalf of all Marketing Authorisation holders (see Annex I) has applied for harmonisation according to Article 30 of Directive 2001/83/EC, as amended, of their products Prograf and associated names 0.5, 1 and 5 mg hard capsules (oral use) and Prograf and associated names 5 mg/ml concentrate for infusion (intravenous use).

Quality aspects do not form part of the current arbitration procedure. However, the following efficacy and safety issues were addressed:

- Efficacy issues

Kidney transplantation:

The efficacy of tacrolimus for kidney transplantation has been investigated in a number of studies and different regimens and can nowadays be regarded as a well-established treatment option, both for primary immunosuppression and for rescue therapy.
Small numbers of children were included in various trials; however, there also exists one randomised controlled (vs. cyclosporine micro-emulsion and in combination with corticosteroids and azthioprine) 6-months paediatric study. One pitfall for the renal paediatric indication is, however, the lack of long-term data. This should be dealt with as a follow-up request.

Heart transplantation in adults:

Tacrolimus has established itself as an alternative to cyclosporine in cardiac transplant immunosuppression. This has been done mainly by long time experience with the drug at different centres in Europe and the US. Data from **"**The Registry of the International Society for Heart and Lung Transplantation" (ISHLT) confirm the findings of the MAH's pivotal study in primary heart transplantation as well as the results of an array of small, single centre, open, randomized/non-randomized studies. Based on these data the efficacy of tacrolimus appears to be well established.

In treatment of acute rejection the therapeutic regimen with tacrolimus has been proven to provide either a significantly improved histological endomyocardial biopsy grading of rejection or a resolution of rejection. Most of the data supporting this indication are as expected retrospective. But in a scenario where re-transplantation or death is a likely outcome a more liberal attitude toward the indication is in place.

Heart transplantation in paediatric patients:

Data on cardiac transplantation in children are sparse due to the low number of transplantations performed each year. The ISHLT's annual report therefore adds important information to the use of heart transplantation in children. As shown in both the published data and the ISHLT's annual report tacrolimus can substitute ciclosporin as primary immunosuppression therapy.

In treatment of acute rejection the therapeutic regiment with tacrolimus has been proven to provide either a significantly improved histological endomyocardial biopsy grading of rejection or a resolution of rejection. Most of the data supporting this indication are as expected retrospective. But in a scenario

where re-transplantation or death is a likely outcome a more liberal attitude toward the indication is in place.

Liver transplantation:

There is consistent evidence across many small and some moderate sized clinical trials that tacrolimus is an effective maintenance immunosuppressant when used as part of a multi-agent regimen. In head to head comparisons with ciclosporin it appears to have a modest efficacy advantage. That contention is also supported by a greater number of patients who need rescue therapy switching from ciclosporin to tacrolimus than the other way around. It would seem appropriate to recognise the *de facto* situation that tacrolimus is used in primary and rescue situations as an immunosupressant in liver transplantation and grant an appropriate therapeutic indication.

Other allografts (lung, pancreas and intestines)

Dosage recommendations are provided for rejection therapy, concerning "other allografts". These dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data.

Several amendments to the SPC were introduced, in particular pertaining clinical indications (4.1) and the section on posology and method of administration (4.2).

In addition, findings on clinical pharmacology were introduced in the sections on special warnings and precautions for use (4.4), interaction with other medicinal products and other forms of interaction (4.5) and the section on pharmacokinetic properties (5.2).

- Safety issues

The safety database for tacrolimus is fragmented and uncertain. The clinical trials conducted in indications other than liver and kidney transplantation have been quite small and seem to have been investigator driven rather then driven by the MAH. Even the trials in liver and kidney transplantation were of only moderate size.

Of note is the probable greater propensity of tacrolimus and ciclosporin to cause glucose intolerance and clinically manifest diabetes mellitus.

The consequences of long-term immunosuppression, infections and tumour formation, are likely to increase with time, but this issue was not addressed. Only anecdotal descriptions of isolated patients or small numbers of patients in differing organ transplant indications were provided. The long-term safety profile of tacrolimus has not been systematically studied.

Several amendments to various sections of the SPC were introduced. Section on contraindications (4.3) remained unchanged. A wording modification was introduced to section on pregnancy and lactation (4.6) in order to add clarity and to put it in line with the guideline on summary of product characteristics. Inconsistencies between section 4.6 (Pregnancy and lactation) and section 5.3 (Preclinical safety data) have been corrected and more information has been included on male fertility. Section on undesirable effects (4.8) was brought in line with the guideline on summary of product characteristics. Classification and terminology were amended according to the MedDRA system organ class.

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Prograf and associated names is favourable for use relating to:

- Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.

- Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

The divergences identified at the start of the referral have been resolved.

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic, Labelling and Package Leaflet proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, Labelling and Package Leaflet are set out in Annex III of the CHMP Opinion for Prograf and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 0.5 mg hard capsules
Prograf and associated names (see Annex I) 1 mg hard capsules
Prograf and associated names (see Annex I) 5 mg hard capsules

[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[To be completed nationally]

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

<Invented name> 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 transplant patients.

General considerations
The recommended initial dosages presented below are intended to act solely as a guideline. <Invented name> dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below for recommended target whole blood trough concentrations). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.
<Invented name> 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.
<Invented name> is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The <Invented name> 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).

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 <Invented name> 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 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 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.
Dose adjustment during post-transplant period in adults and children
<Invented name> doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to <Invented name> 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 <Invented name> 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 <Invented name> may need to be reduced.
For conversion to <Invented name>, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from ciclosporin to <Invented name>, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Kidney transplantation
Prophylaxis of transplant rejection – adults
Oral <Invented name> 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 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 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
<Invented name> doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to <Invented name>-based dual-therapy. 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 <Invented name> 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 <Invented name> may need to be reduced.
For conversion to <Invented name>, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from ciclosporin to <Invented name>, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation
Prophylaxis of transplant rejection – adults

<Invented name> can be used with antibody induction (allowing for delayed start of <Invented name> therapy) or alternatively in clinically stable patients without antibody induction.
Following antibody induction, oral <Invented name> 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 stabilised. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 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
<Invented name> has been used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if <Invented name> 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 <Invented name> 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
<Invented name> 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 <Invented name> 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 <Invented name>, 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 <Invented name>, 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 ciclosporin to <Invented name>, 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 <Invented name> 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 specific patient populations
Patients with liver impairment
Dose reduction may be necessary in patients with severe liver impairment in order to maintain the blood trough levels within the recommended target range.
Patients with kidney impairment
As the pharmacokinetics of tacrolimus are unaffected by renal function, no dose adjustment should be required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).
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 ciclosporin

Care should be taken when converting patients from ciclosporin-based to <Invented name>-based therapy (see sections 4.4 and 4.5). <Invented name> therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, <Invented name> therapy has been initiated 12 - 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Target whole blood trough concentration recommendations
Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient.
As an aid to optimise 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 <Invented name> 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.

4.4 Special warnings and precautions for use

During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.
Herbal preparations containing St. John's Wort (Hypericum perforatum) or other herbal preparations should be avoided when taking <Invented name> due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus (see section 4.5 Interactions with other medicinal products and other forms of interactions).
Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.

The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.5).

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children with

tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of <Invented name> therapy, 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.

Patients treated with <Invented name> have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to <Invented name> therapy should not receive anti-lymphocyte treatment concomitantly. Very young (< 2 years), EBV-VCA-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with <Invented name>. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma.

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Metabolic interactions
Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is therefore recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A metabolism 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).

Inhibitors of metabolism
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.
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, norethindrone, quinidine, tamoxifen, (triacetyl)oleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.

Inducers of metabolism
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 metabolised by CYP3A4 may affect the metabolism of such medicinal products.
The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.4).
Tacrolimus has been shown to increase the blood level of phenytoin.
As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.
Limited knowledge of interactions between tacrolimus and statins is available. Available data suggests that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.
Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

Other interactions which have led 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, cotrimoxazole, NSAIDs, ganciclovir or aciclovir).
Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.
As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone) should be avoided.
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.

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

4.6 Pregnancy and lactation

Human data show that tacrolimus is able to 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. Due to the need of treatment, tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. 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) as well as for hyperkalaemia in the newborn, which, however, normalizes spontaneously.
In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3). Tacrolimus affected male fertility in rats (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 <Invented name>.

4.7 Effects on ability to drive and use machines

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if <Invented name> is administered in association with alcohol.

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. Oral administration appears to be associated with a lower incidence of adverse drug reactions compared with intravenous use. Adverse drug reactions are listed below in descending order by frequency of occurrence: 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, including isolated reports).

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 pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Neoplasms benign, malignant and unspecified
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.

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

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

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

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

Nervous system disorders

very common:	tremor, headache
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

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

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

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, gastrooesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

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

Skin and subcutaneous 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

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

Reproductive system and breast disorders
uncommon: dysmenorrhoea and uterine bleeding

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, chest tightness, mobility decreased, ulcer
very rare: fat tissue increased

Injury, poisoning and procedural complications
common: primary graft dysfunction

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, increased blood urea nitrogen and elevated serum creatinine concentrations, and increase in alanine aminotransferase levels.
No specific antidote to <Invented name> 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 dialysable. 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: Macrolide immunosuppressant, ATC code: L04A A05

Mechanism of action and pharmacodynamic effects
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 lymphokine 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.

Results from published data in other primary organ transplantation

<Invented name> has evolved into an accepted treatment as primary immunosuppressive medicinal product following pancreas, lung and intestinal 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 summarised below.

Lung transplantation

The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomisation to either tacrolimus or ciclosporin. 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 ciclosporin-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 ciclosporin group (Treede et al., 3rd ICI San Diego, US, 2004;Abstract 22).

Another randomised study included 66 patients on tacrolimus versus 67 patients on ciclosporin. 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 ciclosporin 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 ciclosporin group (1.09 episodes). Obliterative bronchiolitis developed in 21.7% of patients in the tacrolimus group compared with 38.0% of patients in the ciclosporin group ($p = 0.025$). Significantly more ciclosporin-treated patients ($n = 13$) required a switch to tacrolimus than tacrolimus-treated patients to ciclosporin ($n = 2$) ($p = 0.02$) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomised to the tacrolimus versus 24 patients to the ciclosporin 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 ciclosporin 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%) (Treede et al., J Heart Lung Transplant 2001;20:511).

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 randomised to tacrolimus (n=103) or to ciclosporin (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 ciclosporin ($p < 0.0005$), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from ciclosporin to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy (Bechstein et al., Transplantation 2004;77:1221).

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 (Abu-Elmagd et al., Ann Surg 2001;234:404).

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 <Invented name> capsules peak concentrations (C_{max}) 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 tarolimus is in the range of 20% - 25%.

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

In healthy subjects, <Invented name> 0.5 mg, <Invented name> 1 mg and <Invented name> 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 both 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 <Invented name> was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.

In a study of stable renal transplant patients who were administered <Invented name> immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption of <Invented name>.

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.

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. Paediatric liver transplant recipients have a TBC approximately twice that of adult liver transplant patients. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism are considered to be responsible for the higher clearance rates observed following transplantation.

The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours. In adult and paediatric liver transplant patients, it averaged 11.7 hours and 12.4 hours, respectively, compared with 15.6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

Metabolism and biotransformation

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4. Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one

of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to pharmacological activity of tacrolimus.

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

5.3 Preclinical safety data

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
[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

[To be completed nationally]

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)
[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 5 mg/ml concentrate for solution for infusion

[see Annex I - to be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[To be completed nationally]

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

<Invented name> 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 transplant patients.

General considerations
The recommended initial dosages presented below are intended to act solely as a guideline. <Invented name> dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below for recommended target whole blood trough concentrations). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.
<Invented name> 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. <Invented name> is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The <Invented name> dose may vary depending upon the immunosuppressive regimen chosen.

Method of administration
The concentrate should be used for intravenous infusion only after it is diluted with suitable carrier media (see section 6.6).

Duration of dosing
Patients should be converted from intravenous to oral medication as soon as individual circumstances permit. Intravenous therapy should not be continued for more than 7 days.

Dosage recommendations – Liver transplantation

Prophylaxis of transplant rejection - adults
Oral <Invented name> 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 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 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.
Dose adjustment during post-transplant period in adults and children
<Invented name> doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to <Invented name> 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 <Invented name> 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 <Invented name> may need to be reduced.
For conversion to <Invented name>, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from ciclosporin to <Invented name>, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Kidney transplantation
Prophylaxis of transplant rejection – adults
Oral <Invented name> 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 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 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
<Invented name> doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to <Invented name>-based dual-therapy. 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 <Invented name> 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 <Invented name> may need to be reduced.
For conversion to <Invented name>, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from ciclosporin to <Invented name>, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation
Prophylaxis of transplant rejection – adults
<Invented name> can be used with antibody induction (allowing for delayed start of <Invented name> therapy) or alternatively in clinically stable patients without antibody induction.
Following antibody induction, oral <Invented name> 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 stabilised. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 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
<Invented name> has been used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if <Invented name> 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 <Invented name> 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
<Invented name> 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 <Invented name> 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 <Invented name>, 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 <Invented name>, 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 ciclosporin to <Invented name>, 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 <Invented name> 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 specific patient populations
Patients with liver impairment
Dose reduction may be necessary in patients with severe liver impairment in order to maintain the blood trough levels within the recommended target range.
Patients with kidney impairment
As the pharmacokinetics of tacrolimus are unaffected by renal function, no dose adjustment should be required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).
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 ciclosporin
Care should be taken when converting patients from ciclosporin-based to <Invented name>-based therapy (see sections 4.4 and 4.5). <Invented name> therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, <Invented name> therapy has been

initiated 12 - 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Target whole blood trough concentration recommendations
Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient.
As an aid to optimise 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 <Invented name> 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 <*To be implemented nationally* - in particular polyoxyethylene hydrogenated castor oil or structurally related compounds.>

4.4 Special warnings and precautions for use

During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.
Herbal preparations containing St. John's wort (Hypericum perforatum) or other herbal preparations should be avoided when taking <Invented name> due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus (see section 4.5 Interactions with other medicinal products and other forms of interactions).
Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.

The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.5).

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and

oedema. Accordingly, high-risk patients, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of <Invented name> therapy, 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.

Patients treated with <Invented name> have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to <Invented name> therapy should not receive anti-lymphocyte treatment concomitantly. Very young (< 2 years), EBV-VCA-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with <Invented name>. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma.

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

If administered accidentally either arterially or perivasally, the reconstituted <Invented name> 5 mg/ml Concentrate for Solution for Infusion may cause irritation at the injection site.
[*To be implemented nationally*]
<<Invented name> 5 mg/ml Concentrate for Solution for Infusion contains polyoxyethylene hydrogenated castor oil, which has been reported to cause anaphylactoid reactions. Caution is therefore necessary in patients who have previously received preparations containing polyoxyethylene castor oil derivatives either by intravenous injection or infusion, and in patients with an allergenic predisposition. The risk of anaphylaxis may be reduced by slow infusion of reconstituted <Invented name> 5 mg/ml Concentrate for Solution for Infusion or by the prior administration of an antihistamine.
The ethanol content (638 mg per ml) of <Invented name> 5mg/ml Concentrate for Solution for Infusion should be taken into account.>

4.5 Interaction with other medicinal products and other forms of interaction

Metabolic interactions
Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is therefore recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A metabolism 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).

Inhibitors of metabolism
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.

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, norethindrone, quinidine, tamoxifen, (triacetyl)oleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.

Inducers of metabolism
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 metabolised by CYP3A4 may affect the metabolism of such medicinal products.
The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.4).
Tacrolimus has been shown to increase the blood level of phenytoin.
As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.
Limited knowledge of interactions between tacrolimus and statins is available. Available data suggests that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.
Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

Other interactions which have led 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, cotrimoxazole, NSAIDs, ganciclovir or aciclovir).
Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.
As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone) should be avoided.
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.

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

4.6 Pregnancy and lactation

Human data show that tacrolimus is able to 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. Due to the need of treatment, tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived

benefit justifies the potential risk to the foetus. 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) as well as for hyperkalaemia in the newborn, which, however, normalizes spontaneously.
In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3). Tacrolimus affected male fertility in rats (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 <Invented name>.

4.7 Effects on ability to drive and use machines

Not relevant.

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. Oral administration appears to be associated with a lower incidence of adverse drug reactions compared with intravenous use. Adverse drug reactions are listed below in descending order by frequency of occurrence: 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, including isolated reports).

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 pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Neoplasms benign, malignant and unspecified
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.

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

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

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

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

Nervous system disorders

very common:	tremor, headache
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

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

Vascular disorders

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

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, gastrooesophageal reflux disease, impaired gastric emptying
rare:	subileus, pancreatic pseudocyst

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

Skin and subcutaneous 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

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

Reproductive system and breast disorders

uncommon:	dysmenorrhoea and uterine bleeding

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, chest tightness, mobility decreased, ulcer
very rare:	fat tissue increased

Injury, poisoning and procedural complications

common:	primary graft dysfunction

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, increased blood urea nitrogen and elevated serum creatinine concentrations, and increase in alanine aminotransferase levels.
No specific antidote to <Invented name> 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 dialysable. 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: Macrolide immunosuppressant, ATC code: L04A A05

Mechanism of action and pharmacodynamic effects

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 lymphokine 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.

Results from published data in other primary organ transplantation

<Invented name> has evolved into an accepted treatment as primary immunosuppressive medicinal product following pancreas, lung and intestinal 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 summarised below.

Lung transplantation

The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomisation to either tacrolimus or ciclosporin. 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 ciclosporin-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 ciclosporin group (Treede et al., 3rd ICI San Diego, US, 2004;Abstract 22).

Another randomised study included 66 patients on tacrolimus versus 67 patients on ciclosporin. 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 ciclosporin 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 ciclosporin group (1.09 episodes). Obliterative bronchiolitis developed in 21.7% of patients in the tacrolimus group compared with 38.0% of patients in the ciclosporin group ($p = 0.025$). Significantly more ciclosporin-treated patients ($n = 13$) required a switch to tacrolimus than tacrolimus-treated patients to ciclosporin ($n = 2$) ($p = 0.02$) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomised to the tacrolimus versus 24 patients to the ciclosporin 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 ciclosporin 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%) (Treede et al., J Heart Lung Transplant 2001;20:511).

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 randomised to tacrolimus ($n=103$) or to ciclosporin ($n=102$). 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 ciclosporin ($p < 0.0005$), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from ciclosporin to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy (Bechstein et al., Transplantation 2004;77:1221).

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 (Abu-Elmagd et al., Ann Surg 2001;234:404).

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 <Invented name> capsules peak concentrations (C_{max}) 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 tarolimus is in the range of 20% - 25%.

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

In healthy subjects, <Invented name> 0.5 mg, <Invented name> 1 mg and <Invented name> 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 both 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 <Invented name> was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.

In a study of stable renal transplant patients who were administered <Invented name> immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption of <Invented name>.

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.

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. Paediatric liver transplant recipients have a TBC approximately twice that of adult liver transplant patients. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of

tacrolimus, or corticosteroid-induced increased metabolism are considered to be responsible for the higher clearance rates observed following transplantation.
The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours. In adult and paediatric liver transplant patients, it averaged 11.7 hours and 12.4 hours, respectively, compared with 15.6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

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

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

5.3 Preclinical safety data

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

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

[To be completed nationally]

11. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

14. DATE OF REVISION OF THE TEXT

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 0.5 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 0.5 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL 0.5 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 0.5 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch: {number}

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM WRAPPER 0.5 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prograf and associated names (see Annex I) 0.5 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch: {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 1 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 1 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL 1 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 1 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch: {number}

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM WRAPPER 1 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prograf and associated names (see Annex I)1 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch: {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 5 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 5 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL 5 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 5 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch: {number}

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM WRAPPER 5 mg CAPSULES

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prograf and associated names (see Annex I) 5 mg hard capsules
[See Annex I – To be completed nationally]
Tacrolimus
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch: {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 5 mg/ml CONCENTRATE FOR SOLUTION FOR INFUSION

1. NAME OF THE MEDICINAL PRODUCT

Prograf and associated names (see Annex I) 5 mg/ml concentrate for solution for infusion
[See Annex I – to be completed nationally]
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
[Method of administration to be completed nationally]
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}
After reconstitution: [To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
AMPOULE LABEL 5 mg/ml CONCENTRATE FOR SOLUTION FOR INFUSION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prograf and associated names (see Annex I) 5 mg/ml concentrate for solution for infusion
[See Annex I – to be completed nationally]
Tacrolimus
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch: {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

[To be completed nationally]

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Prograf and associated names (see Annex I) 0.5 mg hard capsules
Prograf and associated names (see Annex I) 1 mg hard capsules
Prograf and associated names (see Annex I) 5 mg hard capsules

[See Annex I – to be completed nationally]
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 <INVENTED NAME> IS AND WHAT IT IS USED FOR

<Invented name> belongs to a group of medicines called immunosuppressants. Following your organ transplant (e.g. liver, kidney, heart), your body's immune system will try to reject the new organ. <Invented name> is used to control your body's immune response enabling your body to accept the transplanted organ.
<Invented name> is often used in combination with other medicines that also suppress the immune system.

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

2. BEFORE YOU TAKE <INVENTED NAME>

Do not take <Invented name>
- If you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of <Invented name>.
- If you are allergic (hypersensitive) to any antibiotic belonging to the subgroup of macrolide antibiotics.

Take special care with <Invented name>
- You will need to take <Invented name> every day as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.
- Whilst you are taking <Invented name> your doctor may want to carry out a number of tests (including blood, urine, heart function, visual and neurological tests) from time to time. This is quite normal and will help your doctor to decide on the most appropriate dose of <Invented name> for you.

- Please avoid taking any herbal remedies, e.g. St. John's wort (Hypericum perforatum) or any other herbal products as this may affect the effectiveness and the dose of <Invented name> that you need to receive. If in doubt please consult your doctor prior to taking any herbal products or remedies.
- If you have liver problems or have had a disease which may have affected your liver, please tell your doctor as this may affect the dose of <Invented name> that you receive.
- If you have diarrhoea for more than one day, please tell your doctor, because it might be necessary to adapt the dose of <Invented name> that you receive.
- In view of the potential risk of malignant skin changes with immunosuppressive therapy, you should wear appropriate protective clothing and use a sunscreen with a high sun protection factor to limit your exposure to sunlight and UV light.
- If you need to have any vaccinations, please inform your doctor beforehand. Your doctor will advise you on the best course of action.

Taking 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 remedies.
<Invented name> blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking <Invented name> which may require and increase or decrease in <Invented name> dose. In particular, you should tell your doctor if you are taking or have recently taken medicines with active substances like:
- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g. ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, erythromycin, clarithromycin, josamycin, and rifampicin
- HIV protease inhibitors e.g ritonavir
- the anti-ulcer substance omeprazole
- hormone treatments with ethinylestradiol (e.g the oral contraceptive pill) or danazol
- medicines for high blood pressure or heart problems such as nifedipine, nicardipine, diltiazem and verapamil
- medicines known as "statins" used to treat elevated cholesterol and triglycerides
- the anti-epileptic medicines phenytoin or phenobarbital
- the corticosteroids prednisolone and methylprednisolone
- the anti-depressant nefazodone
- St. John's Wort (hypericum perforatum)

<Invented name> must not be taken with ciclosporin.

Your doctor also needs to know if you are taking potassium supplements or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone), certain pain killers (so-called NSAIDs, e.g. ibuprofen), anticoagulants, or oral medication for diabetic treatment, while you take <Invented name>.

The use of ibuprofen, amphotericin B, antivirals (e.g. aciclovir), may worsen kidney or nervous system problems when taken together with <Invented name>.

Taking <Invented name> with food and drink
You should generally take <Invented name> on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal. Grapefruit and grapefruit juice should be avoided while taking <Invented name>.

Pregnancy and breast-feeding
If you plan to become pregnant or think that you may be pregnant, ask your doctor or pharmacist for advice before taking any medicine.
<Invented name> is excreted into breast milk. Therefore you should not breast-feed whilst receiving <Invented name>.

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 <Invented name>. These effects are more frequently observed if <Invented name> is taken in conjunction with alcohol use.

3. HOW TO TAKE <INVENTED NAME>

Always take <Invented name> exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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 <Invented name> dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take and how often.

<Invented name> is taken orally twice daily, usually in the morning and evening. The capsules should be swallowed whole with a glass of water. Do not swallow the desiccant contained in the foil wrapper.

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

If you forget to take <Invented name>
Do not take a double dose to make up for forgotten individual doses.
If you have forgotten to take your <Invented name> capsules, wait until it is time for the next dose, and then continue as before.

If you stop taking <Invented name>
Stopping your treatment with <Invented name> 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, <Invented name> can cause side effects, although not everybody gets them.

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.

<Invented name> reduces your body's own defense mechanism to stop you rejecting your transplanted organ. Consequently, your body will not be as good as usual at fighting infections. Therefore you may be more prone to infections than usual while you are taking <Invented name>.

Severe effects have been reported, including allergic and anaphylactic reactions. Benign and malignant tumours have been reported following <Invented name> treatment as a result of immunosuppression.

Blood and lymph disorders

common:	reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts
uncommon:	changes in blood clotting, reduction in all blood cell counts
rare:	small bleedings in your skin due to blood clots

Metabolism and nutrition disorders

very common:	increased blood sugar, diabetes mellitus, increased potassium in the blood
common:	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
uncommon:	dehydration, reduced protein or sugar in the blood, increased phosphate in the blood

Psychiatric disorders

very common:	difficulty in sleeping
common:	anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders

Nervous system disorders

very common:	trembling, headache
common:	fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
uncommon:	coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
rare:	increased muscle stiffness
very rare:	muscular weakness

Eye disorders

common:	blurred vision, increased sensitivity to light, eye disorders
uncommon:	opacity of the lens
rare:	blindness

Ear disorders

common:	ringing sound in your ears
uncommon:	impaired hearing
rare:	deafness

Heart disorders

common:	reduced blood flow in the heart vessels, faster heartbeat
uncommon:	irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
rare:	collection of fluid around the heart
very rare:	echocardiogram abnormal

Blood vessel disorders

very common:	increased blood pressure
common:	bleeding, partial or complete blocking of blood vessels, reduced blood pressure

uncommon: blood clot in a vein of a limb, shock

Respiratory tract disorders
common: shortness in breath, changes in the lung tissue, collection of liquid around the lung, inflammation of the pharynx, cough, flu-like symptoms
uncommon: difficulties in breathing, respiratory tract disorders, asthma
rare: acute breathlessness

Gastrointestinal disorders
very common: diarrhoea, nausea
common: 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, flatulence, bloating, loose stools, stomach problems
uncommon: obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
rare: cyst formation in your pancreas

Liver and gall bladder disorders
common: changes in liver enzymes and function, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
rare: problems with blood flow in the liver
very rare: liver failure, narrowing of the bile vessel

Skin disorders
common: itching, rash, hair loss, acne, increased sweating
uncommon: dermatitis, burning sensation in the sunlight
rare: serious illness with blistering of skin, mouth, eyes and genitals, increased hairiness

Bone and joint disorders
common: pain in joints, limbs or back, muscle cramps
uncommon: joint disorders

Disorders of kidney, urinary system and genitals
very common: kidney problems
common: insufficient function of the kidneys, reduced production of urine, impaired or painful urination
uncommon: inability to urinate, painful menstruation and abnormal menstrual bleeding
very rare: painful urination with blood in the urine

Disorders affecting the body as a whole
common: general weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling of temperature disturbed
uncommon: 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: thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer
very rare: increase of fat tissue

Disorders of your transplanted organ
common: insufficient function of your transplanted organ

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 <INVENTED NAME>

Keep out of the reach and sight of children.

Do not use <Invented name> after the expiry date which is stated on the carton after {abbreviation used for expiry date [To be completed nationally]}. The expiry date refers to the last day of that month.

[To be completed nationally]

6. FURTHER INFORMATION

What <Invented name> contains

- The active substance is tacrolimus
- The other ingredients are [To be completed nationally].

What <Invented name> looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following name:

Prograf:
Austria, Cyprus, Czech Republic, Denmark, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Norway, Poland, Portugal, Slovakia, Slovenia, Sweden,United Kingdom.

Prograft:
Belgium, Luxembourg, The Netherlands.

This leaflet was last approved in {MM/YYYY}.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Prograf and associated names (see Annex I) 5 mg/ml concentrate for solution for infusion
[See Annex I – to be completed nationally]
Tacrolimus

Read all of this leaflet carefully before you start using 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 <INVENTED NAME> IS AND WHAT IT IS USED FOR

<Invented name> belongs to a group of medicines called immunosuppressants. Following your organ transplant (e.g. liver, kidney, heart), your body's immune system will try to reject the new organ. <Invented name> is used to control your body's immune response enabling your body to accept the transplanted organ.
<Invented name> is often used in combination with other medicines that also suppress the immune system.

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

2. BEFORE YOU USE <INVENTED NAME>

Do not use <Invented name>
- If you are allergic (hypersensitive) to tacrolimus or to any antibiotic belonging to the subgroup of macrolide antibiotics.
- If you are allergic (hypersensitive) to any of the other ingredients <*To be implemented nationally* - in particular polyoxyethylene hydrogenated castor oil or similar substances.>

Take special care with <Invented name>
- Whilst you are receiving <Invented name> your doctor may want to carry out a number of tests (including blood, urine, heart function, visual and neurological tests) from time to time. This is quite normal and will help your doctor to decide on the most appropriate dose of <Invented name> for you.
- Please avoid taking any herbal remedies, e.g. St. John's wort (Hypericum perforatum) or any other herbal products as this may affect the effectiveness and the dose of <Invented name> that you need to receive. If in doubt please consult your doctor prior to taking any herbal products or remedies.
- If you have liver problems or have had a disease which may have affected your liver, please tell your doctor as this may affect the dose of <Invented name> that you receive.

- If you have diarrhoea for more than one day, please tell your doctor, because it might be necessary to adapt the dose of <Invented name> that you receive.
- In view of the potential risk of malignant skin changes with immunosuppressive therapy, you should wear appropriate protective clothing and use a sunscreen with a high sun protection factor to limit your exposure to sunlight and UV light.
- If you need to have any vaccinations, please inform your doctor beforehand. Your doctor will advise you on the best course of action.

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 remedies.
<Invented name> blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by using <Invented name> which may require and increase or decrease in <Invented name> dose. In particular, you should tell your doctor if you are taking or have recently taken medicines with active substances like:
- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g. ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, erythromycin, clarithromycin, josamycin, and rifampicin
- HIV protease inhibitors e.g ritonavir
- the anti-ulcer substance omeprazole
- hormone treatments with ethinylestradiol (e.g the oral contraceptive pill) or danazol
- medicines for high blood pressure or heart problems such as nifedipine, nicardipine, diltiazem and verapamil
- medicines known as “statins” used to treat elevated cholesterol and triglycerides
- the anti-epileptic medicines phenytoin or phenobarbital
- the corticosteroids prednisolone and methylprednisolone
- the anti-depressant nefazodone
- St. John’s Wort (hypericum perforatum)

<Invented name> must not be used with ciclosporin.

Your doctor also needs to know if you are taking potassium supplements or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone), certain pain killers (so-called NSAIDs, e.g. ibuprofen), anticoagulants, or oral medication for diabetic treatment, while you receive <Invented name>.

The use of ibuprofen, amphotericin B, antivirals (e.g. aciclovir), may worsen kidney or nervous system problems when used together with <Invented name>.

Using <Invented name> with food and drink
Grapefruit and grapefruit juice should be avoided while using <Invented name>.

Pregnancy and breast-feeding
If you plan to become pregnant or think that you may be pregnant, ask your doctor or pharmacist for advice before taking any medicine.
<Invented name> is excreted into breast milk. Therefore you should not breast-feed whilst receiving <Invented name>.

Important information about some of the ingredients of <Invented name>
- <Invented name> contains polyoxyethylene hydrogenated castor oil that may, in a small number of patients, lead to a severe allergic reaction. If you have previously had such a problem, please inform your doctor.
- The alcohol content (638 mg per ml) of <Invented name> 5mg/ml Concentrate for Infusion should be taken into account.

3. HOW TO USE <INVENTED NAME>

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial intravenous doses just after transplantation will generally be in the range of

0.01 – 0.10 mg per kg body weight per day

depending on the transplanted organ.

<Invented name> should be used for intravenous infusion only after it is diluted. You will receive <Invented name> as a continuous 24-hour infusion and never as a short injection.

<Invented name> may cause mild irritation if it is not infused directly into a vein.
Treatment with <Invented name> should not continue for more than 7 days. Your doctor will then prescribe <Invented name> capsules for you instead.

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.

If you receive more <Invented name> than you should
If you have received too much <Invented name>, your doctor will amend your next dose.

If you stop using <Invented name>
Stopping your treatment with <Invented name> 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, <Invented name> can cause side effects, although not everybody gets them.

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.

<Invented name> reduces your body's own defense mechanism to stop you rejecting your transplanted organ. Consequently, your body will not be as good as usual at fighting infections. Therefore you may be more prone to infections than usual while you are taking <Invented name>.

Severe effects have been reported, including allergic and anaphylactic reactions. Benign and malignant tumours have been reported following <Invented name> treatment as a result of immunosuppression.

<u>Blood and lymph disorders</u>

common:	reduction in blood cell counts (platelets, red or white blood cells), inrease in white blood cell counts, changes in red blood cell counts
uncommon:	changes in blood clotting, reduction in all blood cell counts
rare:	small bleedings in your skin due to blood clots

Metabolism and nutrition disorders

very common:	increased blood sugar, diabetes mellitus, increased potassium in the blood
common:	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
uncommon:	dehydration, reduced protein or sugar in the blood, increased phosphate in the blood

Psychiatric disorders

very common:	difficulty in sleeping
common:	anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders

Nervous system disorders

very common:	trembling, headache
common:	fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
uncommon:	coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
rare:	increased muscle stiffness
very rare:	muscular weakness

Eye disorders

common:	blurred vision, increased sensitivity to light, eye disorders
uncommon:	opacity of the lens
rare:	blindness

Ear disorders

common:	ringing sound in your ears
uncommon:	impaired hearing
rare:	deafness

Heart disorders

common:	reduced blood flow in the heart vessels, faster heartbeat
uncommon:	irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
rare:	collection of fluid around the heart
very rare:	echocardiogram abnormal

Blood vessel disorders

very common:	increased blood pressure
common:	bleeding, partial or complete blocking of blood vessels, reduced blood pressure
uncommon:	blood clot in a vein of a limb, shock

Respiratory tract disorders

common:	shortness in breath, changes in the lung tissue, collection of liquid around the lung, inflammation of the pharynx, cough, flu-like symptoms
uncommon:	difficulties in breathing, respiratory tract disorders, asthma
rare:	acute breathlessness

Gastrointestinal disorders

very common:	diarrhoea, nausea
common:	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, flatulence, bloating, loose stools, stomach problems

uncommon: obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
rare: cyst formation in your pancreas

Liver and gall bladder disorders
common: changes in liver enzymes and function, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
rare: problems with blood flow in the liver
very rare: liver failure, narrowing of the bile vessel

Skin disorders
common: itching, rash, hair loss, acne, increased sweating
uncommon: dermatitis, burning sensation in the sunlight
rare: serious illness with blistering of skin, mouth, eyes and genitals, increased hairiness

Bone and joint disorders
common: pain in joints, limbs or back, muscle cramps
uncommon: joint disorders

Disorders of kidney, urinary system and genitals
very common: kidney problems
common: insufficient function of the kidneys, reduced production of urine, impaired or painful urination
uncommon: inability to urinate, painful menstruation and abnormal menstrual bleeding
very rare: painful urination with blood in the urine

Disorders affecting the body as a whole
common: general weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling of temperature disturbed
uncommon: 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: thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer
very rare: increase of fat tissue

Disorders of your transplanted organ
common: insufficient function of your transplanted organ

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 <INVENTED NAME>

Keep out of the reach and sight of children.

Do not use <Invented name> after the expiry date which is stated on the carton after {abbreviation used for expiry date [To be completed nationally]}. The expiry date refers to the last day of that month.

[To be completed nationally]

6. FURTHER INFORMATION

What <Invented name> contains

- The active substance is tacrolimus
- The other ingredients are [To be completed nationally].

What <Invented name> looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following name:

Prograf:
Austria, Cyprus, Czech Republic, Denmark, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Norway, Poland, Portugal, Slovakia, Slovenia, Sweden,United Kingdom.

Prograft:
Belgium, Luxembourg, The Netherlands

This leaflet was last approved in {MM/YYYY}.