1. NAME OF THE MEDICINAL PRODUCT

tacrolimus cinfa 0.5 mg EFG hard capsules
tacrolimus cinfa 1 mg EFG hard capsules
tacrolimus cinfa 5 mg EFG hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

tacrolimus cinfa 0.5 mg EFG hard capsules
Each capsule contains 0.5 mg of tacrolimus (as monohydrate).
Excipient with known effect: 104.6 mg of anhydrous lactose

tacrolimus cinfa 1 mg EFG hard capsules
Each capsule contains 1 mg of tacrolimus (as monohydrate).
Excipient with known effect: 108.6 mg of anhydrous lactose

tacrolimus cinfa 5 mg EFG hard capsules
Each capsule contains 5 mg of tacrolimus (as monohydrate).
Excipient with known effect: 109.1 mg of anhydrous lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

tacrolimus cinfa 0.5 mg EFG hard capsules
hard capsules
ivory coloured hard gelatine capsules, containing white powder.

tacrolimus cinfa 1 mg EFG hard capsules
hard capsules
white coloured hard gelatine capsules, containing white powder.

tacrolimus cinfa 5 mg EFG hard capsules
hard capsules
red coloured hard gelatine capsules, containing white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of transplant rejection in patients receiving hepatic, renal or cardiac allografts.

Allograft rejection treatment for allografts resistance to other immunosuppressant medications.

4.2 Posology and method of administration

Posology
Treatment with tacrolimus requires careful control performed by properly trained and equipped staff. Only doctors with experience in immunosuppressive therapy and the care of patients with transplants should prescribe this medication and make changes to the immunosuppressant regime.

An involuntary, unintentional or unsupervised change between immediate-release or prolonged-release tacrolimus formulations is dangerous. This may lead to a rejection of the graft or an increase in the incidence of undesirable effects, including low or raised immunosuppresion, due to significant clinical differences in systemic exposure to tacrolimus. Patients must be kept on one unique formulation of tacrolimus with the corresponding daily posology. Changes to the formulation or posology must only be made under the close supervision of a transplant specialist (see sections 4.4 and 4.8). After changing to another alternative formulation, the medication must be monitored and the dose adjusted in order to ensure that systemic exposure to tacrolimus is maintained.

General considerations
The initial recommended dose indicated below is intended to be used as a guide. The tacrolimus cinfa dose must be based primarily on the clinical rejection assessment and the tolerance of each individual patient, with the help of blood level monitoring (see below for recommended target whole blood trough concentrations). If there are symptoms of clinical rejection, changes to the immunosuppressant regime should be considered.
Tacrolimus can be administered orally or intravenously. In general, treatment can be started orally. If necessary, the contents of the capsule can be administered in the form of a suspension in water via a nasogastric tube.
Tacrolimus cinfa is normally administered in combination with other immunosuppressants during the initial post-operation period. The tacrolimus cinfa dose may vary depending on the chosen immunosuppressant regimen.

Method of administration
Dividing the dose and administering it in two doses is recommended (for example, once in the morning and once at night). The capsules must be ingested immediately after being removed from the blister. Patients must be advised to not swallow the desiccant. The capsules must be swallowed with a liquid (preferably water).
In order to achieve maximum absorption, the capsules must generally be administered with an empty stomach or at least one hour before or 2-3 hours after eating food (see section 5.2).

Duration of treatment
In order to avoid rejection of the implant, maintaining immunosuppression is necessary. Therefore, establishing a limit for the duration of oral treatment is impossible.

Dosing recommendations – Hepatic transplant
<u>Prophylaxis of transplant rejection - adults</u>
Oral treatment with tacrolimus cinfa must start with a dose of 0.10-0.20 mg/kg/day, divided into two doses (for example, once in the morning and once at night). Administration must start approximately 12 hours after surgery is completed.
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.
<u>Prophylaxis of transplant rejection – paediatric patients</u>
An initial dose of 0.30 mg/kg/day must be administered, divided into two doses (for example, once in the morning and once at night). If the patient's clinical condition rules out oral administration, an initial intravenous dose of 0.05 mg/kg/day, in the form of a continuous infusion over 24 hours must be administered.
<u>Dose adjustment during post-transplant period in adults and children</u>
The tacrolimus cinfa dose is generally reduced during the post-transplant period. In some cases, withdrawing concomitant immunosuppressant treatment is possible, leading towards tacrolimus

cinfa-based monotherapy. Improvement in the patient's condition after the transplant may affect the pharmacokinetics of tacrolimus and make subsequent adjustments to the dose necessary.

Treatment of the rejection – adult and paediatric patients
High doses of tacrolimus, concomitant treatment with corticosteroids and the introduction of short cycle mono/polyclonal antibodies have been used to treat rejection episodes. If signs of toxicity are noted (e.g. severe adverse reactions, see section 4.8) the dose of tacrolimus cinfa may need to be reduced. For conversion to tacrolimus cinfa, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to tacrolimus cinfa, see below under "Dose adjustments in specific patient populations".

Dosing recommendations – Renal transplant
Prophylaxis of transplant rejection - adults
Treatment with tacrolimus cinfa must start with a dose of 0.20-0.30 mg/kg/day, divided into two doses (for example, once in the morning and once at night). Administration must start approximately 24 hours after surgery is completed.
If it is impossible to administer the medication orally due to the patient's clinical condition, intravenous therapy must be started with 0.05-0.10 mg/kg/day in the form of a continuous 24-hour infusion.
Prophylaxis of transplant rejection – paediatric patients
An initial oral dose of 0.30 mg/kg/day must be administered, divided into two doses (for example, once in the morning and once at night). 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 paediatric patients
The tacrolimus cinfa dose is generally reduced during the post-transplant period. In some case, withdrawing concomitant immunosuppressant treatment is possible, leading towards tacrolimus cinfa-based dual-therapy. Improvement in the patient's condition after the transplant may affect the pharmacokinetics of tacrolimus and make subsequent adjustments to the dose necessary.
Treatment of the rejection – adult and paediatric patients
High doses of tacrolimus, concomitant treatment with corticosteroids and the introduction of short cycle mono/polyclonal antibodies have been used to treat rejection episodes. If signs of toxicity are noted (e.g. severe adverse reactions, see section 4.8) the dose of tacrolimus cinfa may need to be reduced. For conversion to tacrolimus cinfa, treatment should begin with the initial oral dose recommended for primary immunosuppression.
For information on conversion from cyclosporine to tacrolimus cinfa, see below under "Dose adjustments in specific patient populations".

Dosing recommendations – Cardiac transplant
Prophylaxis of transplant rejection - adults
Tacrolimus cinfa can be used with antibody induction (allowing for delayed start of tacrolimus cinfa therapy) or alternatively in clinically stable patients without antibody induction.
Following antibody induction, treatment with tacrolimus cinfa must start with a dose of 0.075 mg/kg/day, divided into two doses (for example, once in the morning and once at night). Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition has 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 has been published where oral tacrolimus was administered within 12 hours post transplantation. This approach is reserved for patients without organ dysfunction (e.g. renal

dysfunction). In this 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 – paediatric patients

Tacrolimus cinfa has been used with or without antibody induction in paediatric heart transplantation.

In patients without antibody induction, if tacrolimus cinfa therapy is initiated intravenously, the initial recommended 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 moved on to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.

Following antibody induction, if tacrolimus cinfa therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (for example, once in the morning and once at night).

Dose adjustment during post-transplant period in adults and paediatric patients

The tacrolimus cinfa dose is generally reduced during the post-transplant period. Improvement in the patient's condition after the transplant may affect the pharmacokinetics of tacrolimus and make subsequent adjustments to the dose necessary.

Treatment of the rejection – adult and paediatric patients

High doses of tacrolimus, concomitant treatment with corticosteroids and the introduction of short cycle mono/polyclonal antibodies have been used to treat rejection episodes.

In adult patients changing to tacrolimus, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (for example, once in the morning and once at night).

In paediatric patients changing to tacrolimus, an initial oral dose of 0.20-0.30 mg/kg/day should be administered in two divided doses (for example, once in the morning and once at night).

For information on conversion from cyclosporine to tacrolimus, 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 transplant patients, tacrolimus has been used at an initial oral dose of 0.10-0.15 mg/kg/day, in pancreas transplant patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplant patients at an initial oral dose of 0.3 mg/kg/day.

Dosage adjustments in specific patient populations

Patients with hepatic failure

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

Patients with renal failure

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 cyclosporine
Care should be taken when converting patients from a cyclosporine-based to a tacrolimus-based therapy (see sections 4.4 and 4.5). Tacrolimus cinfa treatment should be initiated after considering cyclosporine whole blood concentration levels and the patient's clinical condition. Dosing should be delayed in the presence of elevated cyclosporine blood levels. In practice, tacrolimus therapy has been initiated 12 - 24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued following conversion as cyclosporine elimination 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 published literature and individual values established 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-transplant period. When dosed orally, blood trough levels should be analysed approximately 12 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As tacrolimus is a medicinal product with slow clearance, adjustments to the dosage regime 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 tacrolimus levels should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following concomitant administration of substances that 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 of 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 should be maintained in the range of 5 - 15 ng/ml in liver, kidney and heart transplant recipients.

4.3 Contraindications

Known hypersensitivity to tacrolimus or other macrolides or any of the other excipients included in section 6.1.

4.4 Special warnings and precautions for use
During the initial post-transplant period, routine monitoring of the following parameters should be undertaken: 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 regime should be considered.

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects that could be a consequence of either under- or over-exposure to tacrolimus. Patients must be kept on one unique formulation of tacrolimus with the corresponding daily posology. Changes to the formulation or posology must only be made under the close supervision of a transplant specialist (see sections 4.2 and 4.8).

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking tacrolimus cinfa due to the risk of interactions that lead to a decrease in blood tacrolimus concentrations and tacrolimus' reduced clinical effect (see section 4.5 Interactions with other medicinal products and other forms of interactions).

Since blood tacrolimus levels may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.

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

Ventricular hypertrophy or septal hypertrophy, 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 include pre-existing heart disease, use of corticosteroids, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Therefore, high-risk patients, particularly young children and those receiving substantial immunosuppressant treatment should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (for example, initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong QT interval; however, at present there is no substantial evidence to demonstrate it causes Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.

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

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

Patients treated with immunosuppressants, including tacrolimus cinfa, are at increased risk of opportunistic infections (bacterial, fungal, viral and protozoan). Among these conditions are BK virus-associated nephropathy and JC virus-associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or potentially fatal conditions that physicians should consider in differential diagnosing of immunosuppressed patients with deteriorating renal function or neurological symptoms.

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).

This medication contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency (deficiency observed in certain populations in Lapland) or glucose-galactose malabsorption should not take this medication.

4.5 Interaction with other medicinal products and other forms of interaction

Metabolic interactions
Systemically available tacrolimus is metabolised by CYP3A4. There is also evidence of gastrointestinal metabolism through 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. Monitoring tacrolimus blood levels is therefore recommended whenever substances that 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).

Metabolism inhibitors
The following substances have been clinically 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 (for example, 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, norethisterone, quinidine, tamoxifen, troleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.
Lansoprazole and cyclosporine may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

Metabolism inducers
The following substances have been clinically 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 prednisone 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; therefore, 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 cyclosporine is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration

of cyclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporine (see sections 4.2 and 4.4).
Tacrolimus has been shown to increase the level of phenytoin in the blood.
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.
There is limited knowledge regarding the interactions between tacrolimus and statins. Available data suggests that the pharmacokinetics of statins are largely unaltered by the concomitant administration of tacrolimus.
Animal data has shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and phenazone.

Other interactions that have led to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase the toxicity level (for example, aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole/trimethoprim, NSAIDs, ganciclovir or aciclovir).
Increased 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 (for example, amiloride, triamterene, or spironolactone) should be avoided.
Immunosuppressants may affect the response to vaccination; therefore, vaccinations 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 (for example, NSAIDs, oral anticoagulants, or oral anti-diabetics).

4.6 Fertility, pregnancy and lactation

Pregnancy
Human data shows that tacrolimus is able to cross the placenta. Limited data available from organ transplant recipients shows 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 is available. If treatment is necessary, 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 of premature delivery (<37 weeks) as well as of hyperkalaemia in the newborn, which, however, normalizes spontaneously.

Lactation
Human data demonstrates that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breastfeed whilst receiving tacrolimus cinfa.

Fertility
In rats and rabbits, tacrolimus caused embryo-foetal toxicity at doses that demonstrated maternal toxicity (see section 5.3). Tacrolimus affected male fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if tacrolimus cinfa is ingested alongside 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 reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse effects compared with intravenous use. Adverse 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); not known (cannot be estimated from the available data).

Cardiac disorders

Common:	Ischaemic coronary artery disorders, tachycardia
Uncommon:	Ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, abnormal ECG, abnormal heart rate and pulse
Rare:	Pericardial effusion
Very rare:	Abnormal echocardiogram

Blood and lymphatic system disorders

Common:	Anaemia, leucopoenia, thrombocytopenia, leukocytosis, abnormal red blood cell analyses
Uncommon:	Coagulopathies, abnormal coagulation and bleeding analyses, pancytopenia, neutropenia
Rare:	Thrombotic thrombocytopenic purpura, hypoprothrombinaemia

Nervous system disorders

Very common:	Tremor, headache
Common:	Seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, impaired writing, nervous system disorders
Uncommon:	Coma, central nervous system haemorrhages and strokes, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
Rare:	Hypertonia
Very rare:	Myasthenia

Eye disorders

Common:	Blurred vision, photophobia, eye abnormalities
Uncommon:	Cataracts
Rare:	Blindness

Ear and labyrinth disorders

Common:	Tinnitus
Uncommon:	Hypoacusis

Rare: Sensorineural hearing loss
Very rare: Impaired hearing

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, interstitial lung disease, pericardial effusion, pharyngitis, common cold, blocked nose 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, diarrhoea, gastrointestinal signs and symptoms
Uncommon: Paralytic ileus, peritonitis, acute and chronic pancreatitis, increased blood amylase, gastro-oesophageal reflux disease, delayed gastric emptying
Rare: Subileus, pancreatic pseudocyst

Renal and urinary disorders
Very common: Renal failure
Common: Renal failure, acute renal failure, oliguria, renal tubular necrosis, toxic nephropathy, urinary abnormalities, bladder and urethra symptoms
Uncommon: Anuria, haemolytic-uraemic syndrome
Very rare: Nephropathy, haemorrhagic cystitis

Skin and subcutaneous tissue disorders
Common: Itchiness, rash, baldness, acne, increased sweating
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 the extremities, back pain
Uncommon: Joint abnormalities

Endocrine disorders
Rare: Hirsutism

Metabolism and nutrition disorders
Very common: Hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
Common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, decreased appetite, anorexia, metabolic acidosis, hyperlipidaemia, hypercholesterolaemia,

hypertriglyceridaemia, other electrolyte abnormalities

Uncommon: Dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Infections and infestations

As is well known for other potent immunosuppressive agents, patients receiving tacrolimus often face an increased risk of infection (viral, bacterial, fungal, protozoan). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

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

Injury, poisoning and therapeutic procedural complications

Common: Primary graft dysfunction

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

Benign, malignant and unspecified neoplasms (including cysts and polyps)

Patients receiving immunosuppressive treatment are at increased risk of developing neoplasms. Benign and malignant neoplasms, including EBV-associated lymphoproliferative disorders and skin neoplasia, have been reported in association with tacrolimus treatment.

Vascular disorders

Very common:	hypertension
Common:	Haemorrhages, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorder
Uncommon:	Infarction, deep vein thrombosis in the extremities, shock

General disorders and administration site conditions

Common:	Asthenia, febrile disorders, oedema, pain and discomfort, increased blood alkaline phosphate levels, weight gain, body perception disturbance
Uncommon:	Multiple organ dysfunction, flu-like illness, temperature sensitivity, sensation of chest pressure, restlessness, feeling strange, increased blood lactate dehydrogenase, weight loss
Rare:	Thirst, falls, chest tightness, decreased mobility, ulcers
Very rare:	Increased fat tissue

Immune system disorders

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

Hepatobiliary disorders
Common:
hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
Rare:
Hepatic artery thrombosis, hepatic veno-occlusive disease
Very rare:
Hepatic failure, bile duct obstruction

Reproductive system and breast disorders
Uncommon:
Dysmenorrhoea and uterine bleeding

Psychiatric disorders

Very common:	Insomnia
Common:	Mood swings, nightmares, hallucinations, mental disorders
Uncommon:	Psychotic disorders

4.9 Overdose
There is limited experience with regard to overdosing. Several cases of accidental overdosing have been reported; symptoms have included tremors, headaches, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen and high serum creatinine concentrations, and increases in alanine aminotransferase levels.
There is no specific antidote for tacrolimus cinfa. If overdosing occurs, the usual supportive measures and symptomatic treatment should be conducted.

Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma protein binding affinity, it is to be assumed that tacrolimus is not be dialysable. In isolated patients with very high plasma levels, haemofiltration or haemodiafiltration 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: Immunosuppressants. Calcineurin inhibitors, ATC code: L04AD02

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. This leads 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 implant 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 transplants

Tacrolimus has evolved into an accepted treatment as primary immunosuppressive medicinal product following pancreas, lung and intestinal transplants. In prospective published studies tacrolimus was investigated as the primary immunosuppressant in approximately 175 patients following lung transplants, 475 patients following pancreas transplants and 630 patients following intestinal transplants. 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 the primary treatment after liver, kidney and heart transplants. Efficacy results of the largest studies in each indication are summarised below.

Lung transplants

The interim analysis of a recent multicentre study assessed 110 patients who underwent 1:1 randomisation to either tacrolimus or cyclosporine. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus cyclosporine-treated patients (11.5% versus 22.6%) and a lower incidence of chronic rejection, bronchiolitis obliterans syndrome, (2.86% versus 8.57%) was reported within the first year after transplantation. The 1-year patient survival rate was 80.8% in the tacrolimus and 83% in the cyclosporine group (Treede et al., 3rd ICI San Diego, US, 2004; Abstract 22).

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

In an additional two-centre study, 26 patients were assigned randomly to the tacrolimus group whilst 24 patients were assigned randomly to the cyclosporine group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml. The 1-year survival rates were 73.1% in the tacrolimus group versus 79.2% in the cyclosporine group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7% versus 45.8%) and at 1 year after lung transplantation (50% versus 33.3%) (Treede et al., J Heart Lung Transplant 2001; 20:511).

The three studies demonstrated similar survival rates. 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 transplants

A multicentre study included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomised to tacrolimus (n=103) or to cyclosporine (n=102). The initial oral per-protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/mL after Month 6. Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3% versus 74.5% with cyclosporine ($p < 0.0005$), whereas

renal graft survival was similar in both groups. In total, 34 patients changed treatment from cyclosporine to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy (Bechstein et al., Transplantation 2004; 77:1221).

Intestinal transplants

Published clinical experience from a single centre on the use of tacrolimus for primary treatment following intestinal transplants 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 recent years, the initial oral dose of tacrolimus has been 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 men, tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus, 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 linear absorption profile. The mean oral bioavailability of tacrolimus falls within the 20% - 25% range.

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

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

The rate and extent of absorption of tacrolimus is greatest under fasting conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect being most pronounced after a meal high in fat content. The effect of a meal high in carbohydrates is less pronounced.

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

In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast, the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and 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 tacrolimus.

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

Distribution and elimination

In men, the elimination of tacrolimus after intravenous infusion may be described as biphasic.

In systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is mainly bound (> 98.8%) to plasma proteins, particularly to serum albumin and α-1-acid glycoprotein.

Tacrolimus is extensively distributed in the body. The steady-state distribution volume based on plasma concentrations is approximately 1300 l (in 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. Certain 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.
Tacrolimus has a long and variable half-life. 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 extensively metabolised in the liver, primarily by the cytochrome P450-3A4. Considerable metabolisation of tacrolimus also takes place in the intestinal wall. Various metabolites have been identified. Only one of these has been shown to have *in vitro* immunosuppressive activity similar to that of tacrolimus. The other metabolites have either 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 tacrolimus' pharmacological activity.

Elimination
Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in faeces. Approximately 2% of the radioactivity was eliminated in urine. Less than 1% of unmetabolised tacrolimus was detected in urine and faeces, indicating that tacrolimus is almost completely metabolised before elimination; bile is the primary elimination route.

5.3 Preclinical safety data

The kidneys and the pancreas were the primary organs affected in toxicity studies performed on rats and monkeys. In rats, tacrolimus had toxic effects on the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus.
Embryo-foetal toxicity was observed in rats and rabbits; however, this was limited to doses that caused significant toxicity in female animals. In rats, female reproductive function including birth was impaired at toxic dosages and the offspring showed reduced birth weights, viability and growth. In rats, a negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content of the capsule:
Povidone K-30
Croscarmellose Sodium (E-468)
Anhydrous lactose
Magnesium stearate

Capsule film coating:

tacrolimus cinfa 0.5 mg EFG hard capsules:
Titanium dioxide (E-171)
Red ferric oxide (E -172)
Gelatine

tacrolimus cinfa 1 mg EFG hard capsules:
Titanium dioxide (E-171)
Gelatine

tacrolimus cinfa 5 mg EFG hard capsules:
Titanium dioxide (E-171)
Red ferric oxide (E -172)
Gelatine

6.2 Incompatibilities

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

6.3 Shelf life

24 months

After opening the aluminium wrapping: 1 year.

6.4 Special precautions for storage

Do not store at temperatures above 30ºC.
Store in the original packaging to protect tacrolimus cinfa from light and moisture.

6.5 Nature and contents of container
Aluminium PVC/PVDC blister. Blisters with a desiccant in aluminium wrapper.

tacrolimus cinfa 0.5 mg hard capsules
Packages of 20, 30, 50, 60 and 100 hard capsules.

tacrolimus cinfa 1 mg hard capsules
Packages of 20, 30, 50, 60, 90 and 100 hard capsules.

tacrolimus cinfa 5 mg hard capsules
Packages of 30, 50, 60 and 100 hard capsules.

Only some packet sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBERS

tacrolimus cinfa 0.5 mg EFG hard capsules
tacrolimus cinfa 1 mg EFG hard capsules
tacrolimus cinfa 5 mg EFG hard capsules

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

April 2012