

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tacforius 0.5 mg prolonged-release hard capsules

Tacforius 1 mg prolonged-release hard capsules

Tacforius 3 mg prolonged-release hard capsules

Tacforius 5 mg prolonged-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tacforius 0.5 mg prolonged-release hard capsules

Each prolonged-release hard capsule contains 0.5 mg tacrolimus (as monohydrate).

Excipient(s) with known effect

Each capsule contains 53.725 mg lactose

Tacforius 1 mg prolonged-release hard capsules

Each prolonged-release hard capsule contains 1 mg tacrolimus (as monohydrate).

Excipient(s) with known effect

Each capsule contains 107.45 mg lactose

Tacforius 3 mg prolonged-release hard capsules

Each prolonged-release hard capsule contains 3 mg tacrolimus (as monohydrate).

Excipient(s) with known effect

Each capsule contains 322.35 mg lactose

Tacforius 5 mg prolonged-release hard capsules

Each prolonged-release hard capsule contains 5 mg tacrolimus (as monohydrate).

Excipient(s) with known effect

Each capsule contains 537.25 mg lactose

Each capsule contains 0.0154 mg ponceau 4R

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release hard capsule

Tacforius 0.5 mg prolonged-release hard capsules

Gelatin capsules imprinted with “TR” on the light yellow capsule cap and “0.5 mg” on the light orange capsule body

Tacforius 1 mg prolonged-release hard capsules

Gelatin capsules imprinted with “TR” on the white capsule cap and “1 mg” on the light orange capsule body

Tacforius 3 mg prolonged-release hard capsules

Gelatin capsules imprinted with “TR” on the light orange capsule cap and “3 mg” on the light orange capsule body

Tacforius 5 mg prolonged-release hard capsules

Gelatin capsules imprinted with “TR” on the greyish red capsule cap and “5 mg” on the light orange capsule body

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of transplant rejection in adult kidney or liver allograft recipients.

Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.

4.2 Posology and method of administration

Tacforius is a once-a-day oral formulation of tacrolimus. Tacforius therapy requires careful monitoring by adequately qualified and equipped personnel. This medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients.

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

Posology

The recommended initial doses presented below are intended to act solely as a guideline. Tacforius is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The dose may vary depending upon the immunosuppressive regimen chosen. Tacforius dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

In *de novo* kidney and liver transplant patients AUC_{0-24} of tacrolimus for the prolonged-release capsules on Day 1 was 30% and 50% lower respectively, when compared with that for the immediate release capsules at equivalent doses. By Day 4, systemic exposure as measured by trough levels is similar for both kidney and liver transplant patients with both formulations. Careful and frequent monitoring of tacrolimus trough levels is recommended in the first two weeks post-transplant with Tacforius to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, adjustments to the Tacforius dose regimen may take several days before steady state is achieved.

To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the duration of oral therapy can be given.

Prophylaxis of kidney transplant rejection

Tacforius therapy should commence at a dose of 0.20 - 0.30 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery.

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

Prophylaxis of liver transplant rejection

Tacforius therapy should commence at a dose of 0.10 - 0.20 mg/kg/day administered once daily in the morning. Administration should commence approximately 12-18 hours after the completion of surgery.

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

Conversion of tacrolimus immediate release capsule -treated patients to Tacforius

Allograft transplant patients maintained on twice daily immediate release capsules dosing requiring conversion to once daily Tacforius should be converted on a 1:1 (mg:mg) total daily dose basis. Tacforius should be administered in the morning.

In stable patients converted from tacrolimus immediate release capsules (twice daily) to tacrolimus prolonged-release capsules (once daily) on a 1:1 (mg:mg) total daily dose basis, the systemic exposure to tacrolimus (AUC_{0-24}) for tacrolimus prolonged-release capsules was approximately 10% lower than that for tacrolimus immediate release capsules. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for tacrolimus prolonged-release capsules is similar to that of tacrolimus immediate release capsules. When converting from tacrolimus immediate release capsules to Tacforius prolonged-release capsules, trough levels should be measured prior to conversion and within two weeks after conversion. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made to maintain similar systemic exposure. Dose adjustments should be made to ensure that similar systemic exposure is maintained.

Conversion from ciclosporin to tacrolimus

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy (see sections 4.4 and 4.5). The combined administration of ciclosporin and tacrolimus is not recommended. Tacforius 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, tacrolimus-based 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.

Treatment of allograft rejection

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

Treatment of allograft rejection after kidney or liver transplantation

For conversion from other immunosuppressants to once daily Tacforius, treatment should begin with the initial oral dose recommended in kidney and liver transplantation respectively for prophylaxis of transplant rejection.

Treatment of allograft rejection after heart transplantation

In adult patients converted to Tacforius, an initial oral dose of 0.15 mg/kg/day should be administered once daily in the morning.

Treatment of allograft rejection after transplantation of other allografts

Although there is no clinical experience with tacrolimus prolonged-release capsules in lung-, pancreas- or intestine-transplanted patients, tacrolimus immediate release capsules have been used in lung-transplanted patients 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.

Therapeutic drug monitoring

Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring.

As an aid to optimise dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood. 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. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) is similar between the two formulations of tacrolimus prolonged-release capsules and tacrolimus immediate release capsules.

Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Tacrolimus blood trough levels should be determined approximately 24 hours post-dosing of Tacforius, just prior to the next dose. Frequent trough level monitoring in the initial two weeks post transplantation is recommended, followed by periodic monitoring during maintenance therapy. Blood trough levels of tacrolimus should also be closely monitored following conversion from tacrolimus immediate release capsules to Tacforius, dose adjustments, changes in the immunosuppressive regimen, or co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5). The frequency of blood level monitoring should be based on clinical needs. As tacrolimus is a substance with low clearance, following adjustments to the Tacforius dose regimen it may take several days before the targeted steady state is achieved.

Data from clinical studies suggest 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. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5 - 15 ng/ml in liver, kidney and heart transplant recipients.

Special populations

Hepatic impairment

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

Renal impairment

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

Race

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

Gender

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

Elderly

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

Paediatric population

The safety and efficacy of Tacforius in children under 18 years of age have not yet been established. Limited data are available but no recommendation on a posology can be made.

Method of administration

Tacforius is a once-a-day oral formulation of tacrolimus. It is recommended that the oral daily dose of Tacforius be administered once daily in the morning. Tacforius prolonged-release hard capsules should be

taken immediately following removal from the blister. Patients should be advised not to swallow the desiccant. The capsules should be swallowed whole with fluid (preferably water). Tacforius 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). A forgotten morning dose should be taken as soon as possible on the same day. A double dose should not be taken on the next morning.

In patients unable to take oral medicinal products during the immediate post-transplant period, tacrolimus therapy can be initiated intravenously (see Summary of Product Characteristics for tacrolimus 5 mg/ml concentrate for solution for infusion) at a dose approximately 1/5th of the recommended oral dose for the corresponding indication.

4.3 Contraindications

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

Hypersensitivity to other macrolides.

4.4 Special warnings and precautions for use

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (see sections 4.2 and 4.8)

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

For treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients clinical data are not yet available for the prolonged-release formulation of tacrolimus.

For prophylaxis of transplant rejection in adult heart allograft recipients clinical data are not yet available for the prolonged-release formulation of tacrolimus.

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.

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

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking tacrolimus due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity (see section 4.5).

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).

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

Certain combinations of tacrolimus with substances known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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

Gastrointestinal disorders

Gastrointestinal perforation has been reported in patients treated with tacrolimus. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur.

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

Cardiac disorders

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed in patients treated with immediate release tacrolimus on rare occasions and may also occur with prolonged-release capsules. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included preexisting heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9 -12 months). If abnormalities develop, dose reduction of Tacforius, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval and may cause *Torsades de Pointes*. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see section 4.5).

Lymphoproliferative disorders and malignancies

Patients treated with tacrolimus have been reported to develop Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders (see section 4.8). A combination of immunosuppressives such as antilymphocytic antibodies (e.g. basiliximab, daclizumab) given concomitantly increases the risk of EBV associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients 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 Tacforius. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is *per se* not indicative of lymphoproliferative disease or lymphoma.

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

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

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

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

Pure Red Cell Aplasia

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

Special populations

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

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

Excipients

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

Tacforius 5 mg capsules contain ponceau 4R. This may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.

It is strongly recommended to closely monitor tacrolimus blood levels, as well as, QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels

Clinically the following substances have been shown to increase tacrolimus blood levels:

Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir) or HCV protease inhibitors (e.g. telaprevir, boceprevir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced. Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nifedipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, nefazodone and (Chinese) herbal remedies containing extracts of Schisandra sphenanthera.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapson, ergotamine, gestodene, lidocaine, mephentoin, miconazole, midazolam, nilvadipine, norethindrone, quinidine, tamoxifen, (triacyl)oleandomycin. Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.

Lansoprazole and ciclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

Other interactions potentially leading to increased tacrolimus blood levels

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

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

CYP3A4 inducers potentially leading to decreased tacrolimus blood levels

Clinically the following substances have been shown to decrease tacrolimus blood levels:

Strong interactions have been observed with rifampicin, phenytoin, 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. Clinical data suggest 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 leading to clinically detrimental effects

Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, 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 (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse reactions on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In case of in utero exposure, monitoring of the newborn for the potential adverse reactions of tacrolimus is recommended (in particular effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as

well as for hyperkalaemia in the newborn (incidence 8 of 111 neonates, i.e. 7.2 %) which, however normalises spontaneously.

In rats and rabbits, tacrolimus caused embryofetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

Breast-feeding

Human data demonstrate that tacrolimus is excreted in breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving Tacforius.

Fertility

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

4.7 Effects on ability to drive and use machines

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if tacrolimus is administered in association with alcohol.

No studies on the effects of tacrolimus on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

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

The most commonly reported adverse reactions (occurring in > 10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia.

Tabulated list of adverse reactions

The frequency of adverse reactions is defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to < 1/10); uncommon ($\geq 1/1,000$ to < 1/100); rare ($\geq 1/10,000$ to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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.

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 prolonged-release capsules.

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, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leukocytosis
uncommon:	coagulopathies, pancytopenia, neutropenia, coagulation and bleeding analyses abnormal
rare:	thrombotic thrombocytopenic purpura, hypoprothrombinaemia
not known:	pure red cell aplasia, agranulocytosis, haemolytic anaemia

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: diabetes mellitus, hyperglycaemic conditions, hyperkalaemia

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

uncommon: dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia

Psychiatric disorders

very common: insomnia

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

uncommon: psychotic disorder

Nervous system disorders

very common: headache, tremor

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

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

rare: hypertonia

very rare: myasthenia

Eye disorders

common: eye disorders, vision blurred, photophobia

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: heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ventricular hypertrophy, palpitations

rare: pericardial effusion

very rare: *Torsades de Pointes*

Vascular disorders

very common: hypertension

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

uncommon: venous thrombosis deep limb, shock, infarction

Respiratory, thoracic and mediastinal disorders

common: parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal

congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome

Gastrointestinal disorders

very common: diarrhoea, nausea
common: gastrointestinal signs and symptoms, vomiting, gastrointestinal and abdominal pains, gastrointestinal inflammatory conditions, gastrointestinal haemorrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and distension, loose stools
uncommon: acute and chronic pancreatitis, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying
rare: pancreatic pseudocyst, subileus

Hepatobiliary disorders

common: bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice
rare: veno-occlusive liver disease, hepatic artery thrombosis
very rare: hepatic failure

Skin and subcutaneous tissue disorders

common: rash, pruritus, 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, back pain, muscle spasms, pain in limb
uncommon: joint disorders
rare: mobility decreased

Renal and urinary disorders

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

Reproductive system and breast disorders

uncommon: dysmenorrhoea and uterine bleeding

General disorders and administration site conditions

common: febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed
uncommon: influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance
rare: fall, ulcer, chest tightness, thirst
very rare: fat tissue increased

Investigations

very common: liver function tests abnormal
common: blood alkaline phosphatase increased, weight increased
uncommon: amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased
very rare: echocardiogram abnormal, electrocardiogram QT prolonged

Injury, poisoning and procedural complications

common: primary graft dysfunction

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

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

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

Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma protein binding, it is anticipated that 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: Immunosuppressants, calcineurin inhibitors, ATC code: L04AD02

Mechanism of action

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

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

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

Results from clinical trials performed with once-daily tacrolimus prolonged-release capsules

Liver transplantation

The efficacy and safety of tacrolimus prolonged-release capsules and tacrolimus immediate release capsules, both in combination with corticosteroids, was compared in 471 *de novo* liver transplant recipients. The event rate of biopsy confirmed acute rejection within the first 24 weeks after transplantation was 32.6% in the tacrolimus prolonged-release capsules group (N=237) and 29.3% in the tacrolimus immediate release capsules group (N=234). The treatment difference (tacrolimus prolonged-release capsules – tacrolimus immediate release capsules) was 3.3% (95% confidence interval [-5.7%, 12.3%]). The 12-month patient survival rates were 89.2% for tacrolimus prolonged-release capsules and 90.8% for tacrolimus immediate

release capsules; in the tacrolimus prolonged-release capsules arm 25 patients died (14 female, 11 male) and in the tacrolimus immediate release capsules arm 24 patients died (5 female, 19 male). 12-month graft survival was 85.3% for tacrolimus prolonged-release capsules and 85.6% for tacrolimus immediate release capsules.

Kidney transplantation

The efficacy and safety of tacrolimus prolonged-release capsules and tacrolimus immediate release capsules, both in combination with mycophenolate mofetil (MMF) and corticosteroids, was compared in 667 *de novo* kidney transplant recipients. The event rate for biopsy-confirmed acute rejection within the first 24 weeks after transplantation was 18.6% in the tacrolimus prolonged-release capsules group (N=331) and 14.9% in the tacrolimus immediate release capsules group (N=336). The treatment difference (tacrolimus prolonged-release capsules - tacrolimus immediate release capsules) was 3.8% (95% confidence interval [-2.1%, 9.6%]). The 12-month patient survival rates were 96.9% for tacrolimus prolonged-release capsules and 97.5% for tacrolimus immediate release capsules; in the tacrolimus prolonged-release capsules arm 10 patients died (3 female, 7 male) and in the tacrolimus immediate release capsules arm 8 patients died (3 female, 5 male). 12-month graft survival was 91.5% for tacrolimus prolonged-release capsules and 92.8% for tacrolimus immediate release capsules.

The efficacy and safety of tacrolimus immediate release capsules, ciclosporin and tacrolimus prolonged-release capsules, all in combination with basiliximab antibody induction, MMF and corticosteroids, was compared in 638 *de novo* kidney transplant recipients. The incidence of efficacy failure at 12 months (defined as death, graft loss, biopsy-confirmed acute rejection, or lost to follow-up) was 14.0% in the tacrolimus prolonged-release capsules group (N=214), 15.1% in the tacrolimus immediate release capsules group (N=212) and 17.0% in the ciclosporin group (N=212). The treatment difference was -3.0% (tacrolimus prolonged-release capsules - ciclosporin) (95.2% confidence interval [-9.9%, 4.0%]) for tacrolimus prolonged-release capsules vs. ciclosporin and -1.9% (tacrolimus immediate release capsules - ciclosporin) (95.2% confidence interval [-8.9%, 5.2%]) for tacrolimus immediate release capsules vs. ciclosporin. The 12-month patient survival rates were 98.6% for tacrolimus prolonged-release capsules, 95.7% for tacrolimus immediate release capsules and 97.6% for ciclosporin; in the tacrolimus prolonged-release capsules arm 3 patients died (all male), in the tacrolimus immediate release capsules arm 10 patients died (3 female, 7 male) and in the ciclosporin arm 6 patients died (3 female, 3 male). 12-month graft survival was 96.7% for tacrolimus prolonged-release capsules, 92.9% for tacrolimus immediate release capsules and 95.7% for ciclosporin.

Clinical efficacy and safety of tacrolimus immediate release capsules bid in primary organ transplantation

In prospective studies oral tacrolimus immediate release capsules 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 oral tacrolimus immediate release capsules in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus immediate release capsules 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 using oral tacrolimus immediate release capsules 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.

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%).

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 using oral tacrolimus immediate release capsules 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.

Intestinal transplantation

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

5.2 Pharmacokinetic properties

Absorption

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed. Tacforius is a prolonged-release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to maximum blood concentration (C_{max}) of approximately 2 hours (t_{max}).

Absorption is variable and the mean oral bioavailability of tacrolimus (immediate release capsules formulation) is in the range of 20% - 25% (individual range in adult patients 6% - 43%). The oral bioavailability of tacrolimus prolonged-release was reduced when it was administered after a meal. Both the rate and extent of absorption of tacrolimus prolonged-release were reduced when administered with food. Bile flow does not influence the absorption of tacrolimus and therefore treatment with Tacforius may commence orally.

A strong correlation exists between AUC and whole blood trough levels at steady-state for tacrolimus prolonged-release.

Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

Distribution

In man, the disposition of tacrolimus after intravenous infusion may be described as biphasic.

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

Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1300 l (healthy subjects). Corresponding data based on whole blood averaged 47.6 l.

Metabolism

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 the pharmacological activity of tacrolimus.

Excretion

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance 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. 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.

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

5.3 Preclinical safety data

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

When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0.1 to 1.0 mg/kg, QTc prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 ng/ml which is more than 6-fold higher than mean peak concentrations observed with tacrolimus prolonged-release capsules in clinical transplantation.

Embryofoetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic doses and the offspring showed reduced birth weights, viability and growth.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Ethylcellulose

Hypromellose 2910

Lactose monohydrate
Magnesium stearate

Tacforius 0.5 mg prolonged-release hard capsules

Capsule Shell
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Tacforius 1 mg prolonged-release hard capsules

Capsule Shell
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Tacforius 3 mg prolonged-release hard capsules

Capsule Shell
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Tacforius 5 mg prolonged-release hard capsules

Capsule Shell
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Black iron oxide (E172)
Ponceau 4R (E124)
Gelatin

Printing ink

Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Tacrolimus is not compatible with PVC (polyvinylchloride). Tubing, syringes and other equipment used to prepare a suspension of Tacforius capsule contents must not contain PVC.

6.3 Shelf life

Tacforius 0.5 mg and 1 mg prolonged-release hard capsules

2 years

Tacforius 3 mg and 5 mg prolonged-release hard capsules

30 Months

After opening the aluminium wrapper: 1 year

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Transparent PVC/PVDC aluminium blister or perforated unit-dose blister wrapped in an aluminium pouch with a desiccant containing 10 capsules per blister.

Pack sizes: 30, 50, 60 and 100 prolonged-release hard capsules in blisters or 30×1, 50×1, 60×1 and 100×1 prolonged-release hard capsules in perforated unit-dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1244/001
EU/1/17/1244/002
EU/1/17/1244/003
EU/1/17/1244/004
EU/1/17/1244/005
EU/1/17/1244/006
EU/1/17/1244/007
EU/1/17/1244/008
EU/1/17/1244/009
EU/1/17/1244/010
EU/1/17/1244/011
EU/1/17/1244/012
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EU/1/17/1244/019
EU/1/17/1244/020
EU/1/17/1244/021
EU/1/17/1244/022
EU/1/17/1244/023
EU/1/17/1244/024
EU/1/17/1244/025
EU/1/17/1244/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Merckle GmbH
Ludwig-Merckle-Strasse 3
89143 Blaubeuren
Germany

PLIVA Hrvatska d.o.o.
Prilaz baruna Filipovica 25
10 000 Zagreb
Croatia

TEVA Czech Industries s.r.o.
Ostravská 29, č.p. 305
Opava – Komárov
747 70
Czech Republic

Teva Operations Poland Sp. z o.o.
Mogilska 80
31-546 Krakow
Poland

Teva Pharma S.L.U.
C/C, n. 4, Poligono Industrial Malpica
ES-50016 Zaragoza
Spain

Teva Pharmaceutical Works Private Limited Company
Pallagi Ut 13
4042 Debrecen
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tacforius 0.5 mg prolonged-release hard capsules
Tacforius 1 mg prolonged-release hard capsules
Tacforius 3 mg prolonged-release hard capsules
Tacforius 5 mg prolonged-release hard capsules
tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 0.5 mg tacrolimus (as monohydrate).
Each capsule contains 1 mg tacrolimus (as monohydrate).
Each capsule contains 3 mg tacrolimus (as monohydrate).
Each capsule contains 5 mg tacrolimus (as monohydrate).

3. LIST OF EXCIPIENTS

0.5 mg, 1 mg, 3 mg
Contains lactose. See package leaflet for further information.

5mg
Contains lactose and ponceau 4R. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release hard capsules
30×1 prolonged-release hard capsules
50 prolonged-release hard capsules
50×1 prolonged-release hard capsules
60 prolonged-release hard capsules
60×1 prolonged-release hard capsules
100 prolonged-release hard capsules
100×1 prolonged-release hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once daily.
Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

Use all the capsules within 1 year of opening the aluminium wrapping and before the expiry date.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture. This medicinal product does not require any special temperature storage conditions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1244/001 30 capsules
EU/1/17/1244/002 30x1 capsules
EU/1/17/1244/003 50 capsules
EU/1/17/1244/004 50x1 capsules
EU/1/17/1244/005 100 capsules
EU/1/17/1244/006 100x1 capsules
EU/1/17/1244/007 30 capsules
EU/1/17/1244/008 30x1 capsules
EU/1/17/1244/009 50 capsules
EU/1/17/1244/010 50x1 capsules
EU/1/17/1244/011 60 capsules
EU/1/17/1244/012 60x1 capsules
EU/1/17/1244/013 100 capsules
EU/1/17/1244/014 100x1 capsules
EU/1/17/1244/015 30 capsules
EU/1/17/1244/016 30x1 capsules
EU/1/17/1244/017 50 capsules
EU/1/17/1244/018 50x1 capsules
EU/1/17/1244/019 100 capsules
EU/1/17/1244/020 100x1 capsules
EU/1/17/1244/021 30 capsules

EU/1/17/1244/022 30x1 capsules
EU/1/17/1244/023 50 capsules
EU/1/17/1244/024 50x1 capsules
EU/1/17/1244/025 100 capsules
EU/1/17/1244/026 100x1 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tacforius 0.5 mg
Tacforius 1 mg
Tacforius 3 mg
Tacforius 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tacforius 0.5 mg prolonged-release capsules
Tacforius 1 mg prolonged-release capsules
Tacforius 3 mg prolonged-release capsules
Tacforius 5 mg prolonged-release capsules
tacrolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Once daily.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALUMINIUM POUCH

1. NAME OF THE MEDICINAL PRODUCT

Tacforius 0.5 mg prolonged-release capsules
Tacforius 1 mg prolonged-release capsules
Tacforius 3 mg prolonged-release capsules
Tacforius 5 mg prolonged-release capsules
tacrolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP
Use all the capsules within 1 year of opening the aluminium wrapping and before the expiry date.

4. BATCH NUMBER

Lot

5. OTHER

Once daily.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tacforius 0.5 mg prolonged-release hard capsules
Tacforius 1 mg prolonged-release hard capsules
Tacforius 3 mg prolonged-release hard capsules
Tacforius 5 mg prolonged-release hard capsules
tacrolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- 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 only. Do not pass it on to others. It may harm them, even if their signs and illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tacforius is and what it is used for
2. What you need to know before you take Tacforius
3. How to take Tacforius
4. Possible side effects
5. How to store Tacforius
6. Contents of the pack and other information

1. What Tacforius is and what it is used for

Tacforius contains the active substance tacrolimus. It is an immunosuppressant. Following your organ transplant (liver, kidney), your body's immune system will try to reject the new organ. Tacforius is used to control your body's immune response, enabling your body to accept the transplanted organ.

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

Tacforius is used in adults.

2. What you need to know before you take Tacforius

Do not take Tacforius

- if you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Tacforius (see section 6).
- if you are allergic to sirolimus or to any macrolide-antibiotic (e.g. erythromycin, clarithromycin, josamycin).

Warnings and precautions

Tacrolimus immediate release capsules (e.g. Tacni) and Tacforius prolonged-release capsules both contain the active substance, tacrolimus. However, Tacforius prolonged-release capsules are taken once daily, whereas the immediate release capsules are taken twice daily. This is because Tacforius capsules allow for a prolonged-release (more slow release over a longer period) of tacrolimus. Tacforius prolonged-release capsules and tacrolimus immediate release capsules are not interchangeable.

Tell your doctor if any of the following apply to you:

- if you are taking any medicines mentioned below under ‘Other medicines and Tacforius’.
- if you have or have had liver problems
- if you have diarrhoea for more than one day
- if you feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting
- if you have an alteration of the electrical activity of your heart called “QT prolongation”.

Your doctor may need to adjust your dose of Tacforius.

You should keep in regular contact with your doctor. From time to time, your doctor may need to do blood, urine, heart, eye tests, to set the right dose of Tacforius.

You should limit your exposure to the sun and UV (ultraviolet) light whilst taking Tacforius. This is because immunosuppressants could increase the risk of skin cancer. Wear appropriate protective clothing and use a sunscreen with a high sun protection factor.

Children and adolescents

The use of Tacforius is not recommended in children and adolescents under 18 years.

Other medicines and Tacforius

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal preparations.

It is not recommended that Tacforius is taken with ciclosporin (another medicine used for the prevention of transplant organ rejection).

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

- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g. ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, erythromycin, clarithromycin, josamycin, and rifampicin
- HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), used to treat HIV infection
- HCV protease inhibitors (e.g. telaprevir, boceprevir), used to treat hepatitis C infection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- cisapride or the antacid magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill or other hormone treatments with ethinylestradiol, hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g. nifedipine, nicardipine, diltiazem and verapamil)
- anti-arrhythmic medicines (amiodarone) used to control arrhythmia (uneven beating of the heart)
- medicines known as “statins” used to treat elevated cholesterol and triglycerides
- phenytoin or phenobarbital, used to treat epilepsy
- the corticosteroids prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression
- Herbal preparations containing St. John’s Wort (*Hypericum perforatum*) or extracts of *Schisandra sphenanthera*.

Tell your doctor if you are taking or need to take ibuprofen (used to treat fever, inflammation and pain), amphotericin B (used to treat bacterial infections) or antivirals (used to treat viral infections e.g. aciclovir). These may worsen kidney or nervous system problems when taken together with Tacforius.

Your doctor also needs to know if you are taking potassium supplements or certain diuretics used for heart failure, hypertension and kidney disease, (e.g. amiloride, triamterene, or spironolactone), non-steroidal anti-

inflammatory drugs (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes, while you take Tacforius.

If you need to have any vaccinations, please tell your doctor before.

Tacforius with food and drink

Avoid grapefruit (also as juice) while on treatment with Tacforius, since it can affect its levels in the blood.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor for advice before using Tacforius.

Tacforius passes into breast milk. Therefore, you should not breast-feed whilst using Tacforius.

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 Tacforius. These effects are more frequent if you also drink alcohol.

Tacforius contains lactose

Tacforius contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Tacforius 5 mg capsules contains ponceau 4R

Tacforius 5 mg capsules contain ponceau 4R. This may cause allergic reactions.

3. How to take Tacforius

Always take Tacforius exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. This medicine should only be prescribed to you by a doctor with experience in the treatment of transplant patients.

Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine. This medicine should be taken once a day. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

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

0.10 – 0.30 mg per kg body weight per day

depending on the transplanted organ. When treating rejection, these same doses may be used.

Your dose depends on your general condition and on which other immunosuppressive medication you are taking.

Following the initiation of your treatment with Tacforius, frequent blood tests will be taken by your doctor to define the correct dose. Afterwards 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 Tacforius dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take.

You will need to take Tacforius every day as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.

Tacforius is taken orally once daily in the morning. Take Tacforius on an empty stomach or 2 to 3 hours after a meal. Wait at least 1 hour until the next meal. Take the capsules immediately following removal from the

blister. The capsules should be swallowed **whole** with a glass of water. Do not swallow the desiccant contained in the foil pouch.

If you take more Tacforius than you should

If you have accidentally taken too much Tacforius, contact your doctor or nearest hospital emergency department immediately.

If you forget to take Tacforius

If you have forgotten to take your Tacforius capsules in the morning, take them as soon as possible on the same day. Do not take a double dose the next morning.

If you stop taking Tacforius

Stopping your treatment with Tacforius 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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Tacforius can cause side effects, although not everybody gets them.

Tacforius reduces your body's defence mechanism (immune system), which will not be as good at fighting infections. Therefore, you may be more prone to infections while you are taking Tacforius.

Severe effects may occur, including allergic and anaphylactic reactions. Benign and malignant tumours have been reported following Tacforius treatment.

Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), agranulocytosis (a severely lowered number of white blood cells) and haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown) have been reported.

Very common side effects (may affect more than 1 in 10 people)

- Increased blood sugar, diabetes mellitus, increased potassium in the blood
- Difficulty in sleeping
- Trembling, headache
- Increased blood pressure
- Liver function tests abnormal
- Diarrhoea, nausea
- Kidney problems

Common side effects (may affect up to 1 in 10 people)

- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts (seen in blood tests)
- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts (seen in blood tests)
- Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- Fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- Blurred vision, increased sensitivity to light, eye disorders
- Ringing sound in your ears
- Reduced blood flow in the heart vessels, faster heartbeat
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- Shortness in breath, disorders of the respiratory tissues in the lung, collection of liquid around the lung, inflammation of the pharynx, cough, flu-like symptoms

- Stomach problems such as inflammation or ulcer causing abdominal pain or diarrhoea, bleeding in the stomach, inflammation or ulcer in the mouth, collection of fluid in the belly, vomiting, abdominal pain, indigestion, constipation, passing wind, bloating, loose stools
- Bile duct disorders, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- Itching, rash, hair loss, acne, increased sweating
- Pain in joints, limbs or back, muscle spasms
- Insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- General weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling of temperature disturbed
- Insufficient function of your transplanted organ

Uncommon side effects (may affect up to 1 in 100 people)

- Changes in blood clotting, reduction in the number of all types of blood cells (seen in blood tests)
- Dehydration, inability to urinate
- Abnormal blood test results: reduced protein or sugar, increased phosphate, increase of the enzyme lactate dehydrogenase
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- Clouding of the eye lens, impaired hearing
- 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
- Blood clot in a vein of a limb, shock
- Difficulties in breathing, respiratory tract disorders, asthma
- Obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
- Inflammation of the skin, burning sensation in the sunlight
- Joint disorders
- Painful menstruation and abnormal menstrual bleeding
- Multiple organ failure, flu-like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, weight loss

Rare side effects (may affect up to 1 in 1,000 people)

- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Blindness, deafness
- Collection of fluid around the heart
- Acute breathlessness
- Cyst formation in your pancreas
- Problems with blood flow in the liver
- Serious illness with blistering of skin, mouth, eyes and genitals; increased hairiness
- Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer

Very rare side effects (may affect up to 1 in 10,000 people)

- Muscular weakness
- Abnormal heart scan
- Liver failure
- Painful urination with blood in the urine
- Increase of fat tissue

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tacforius

Keep out of the sight and reach of children.

Do not use Tacforius after the expiry date which is stated on the carton and blister after “EXP”. The expiry date refers to the last day of that month. Use all the prolonged-release hard capsules within 1 year of opening the aluminium wrapping.

Store in the original package in order to protect from light and moisture. This medicinal product does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tacforius contains

- The active substance is tacrolimus.
Each capsule of Tacforius 0.5 mg contains 0.5 mg of tacrolimus (as monohydrate).
Each capsule of Tacforius 1 mg contains 1 mg of tacrolimus (as monohydrate).
Each capsule of Tacforius 3 mg contains 3 mg of tacrolimus (as monohydrate).
Each capsule of Tacforius 5 mg contains 5 mg of tacrolimus (as monohydrate).

The other ingredients are:

Capsule content: Hypromellose 2910, ethylcellulose, lactose, magnesium stearate.

Tacforius 0.5 mg, 1 mg & 3 mg prolonged-release hard capsules

Capsule shell: Red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), gelatin

Tacforius 5 mg prolonged-release hard capsules

Capsule Shell: Red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), black iron oxide (E172), ponceau 4R (E124), gelatin

Printing Ink: Shellac, propylene glycol, black iron oxide (E172), potassium hydroxide

What Tacforius looks like and contents of the pack

Tacforius 0.5 mg prolonged-release hard capsules are hard gelatin capsules imprinted with “TR” on the light yellow capsule cap and “0.5 mg” on the light orange capsule body.

Tacforius 0.5 mg is supplied in blisters or perforated unit-dose blisters containing 10 capsules within a protective foil pouch, including a desiccant. Packs of 30, 50 and 100 prolonged-release capsules are available in blisters and packs of 30×1, 50×1 and 100×1 prolonged-release capsules are available in perforated unit-dose blisters.

Tacforius 1 mg prolonged-release hard capsules are hard gelatin capsules imprinted with “TR” on the white capsule cap and “1 mg” on the light orange capsule body.

Tacforius 1 mg is supplied in blisters or perforated unit-dose blisters containing 10 capsules within a protective foil pouch, including a desiccant. Packs of 30, 50, 60 and 100 prolonged-release capsules are available in blisters and packs of 30×1, 50×1, 60×1 and 100×1 prolonged-release capsules are available in perforated unit-dose blisters.

Tacforius 3 mg prolonged-release hard capsules are hard gelatin capsules imprinted with “TR” on the light orange capsule cap and “3 mg” on the light orange capsule body.

Tacforius 3 mg is supplied in blisters or perforated unit-dose blisters containing 10 capsules within a protective foil pouch, including a desiccant. Packs of 30, 50 and 100 prolonged-release capsules are available in blisters and packs of 30×1, 50×1 and 100×1 prolonged-release capsules are available in perforated unit-dose blisters.

Tacforius 5 mg prolonged-release hard capsules are hard gelatin capsules imprinted with “TR” on the greyish red capsule cap and “5 mg” on the light orange capsule body.

Tacforius 5 mg is supplied in blisters or perforated unit-dose blisters containing 10 capsules within a protective foil pouch, including a desiccant. Packs of 30, 50 and 100 prolonged-release hard capsules are available in blisters and packs of 30×1, 50×1 and 100×1 prolonged-release capsules are available in perforated unit-dose blisters.

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>