SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Envarsus 4 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 4 mg tacrolimus (as monohydrate).

Excipient with known effect
Each tablet contains 104 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Oval, white to off-white uncoated tablet, debossed with “4” on one side and “TCS” on the other side.

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

Envarsus is a once-a-day oral formulation of tacrolimus. Tacrolimus therapy requires careful monitoring by adequately qualified and equipped personnel. This medicinal product should only be prescribed, and changes in immunosuppressive therapy be 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 over-immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Posology

The recommended initial doses presented below are intended to act solely as a guideline. Tacrolimus 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.

Envarsus 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.

As tacrolimus is a substance with low clearance, adjustments to the 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.

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

Missed dose
A forgotten dose should be taken as soon as possible on the same day. A double dose should not be taken on the next day.

Prophylaxis of kidney transplant rejection
Envarsus therapy should commence at a dose of 0.17 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery.

Prophylaxis of liver transplant rejection
Envarsus therapy should commence at a dose of 0.11–0.13 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery.
Conversion of Prograf- or Advagraf-treated patients to Envarsus - allograft transplant patients
Envarsus is **not** interchangeable with other existing tacrolimus containing medicinal products (immediate-release or prolonged-release) on an equal dose by dose basis. Allograft transplant patients maintained on twice daily Prograf (immediate-release) or Advagraf (once daily) dosing requiring conversion to once daily Envarsus should be converted on a 1:0.7 (mg:mg) total daily dose basis and the Envarsus maintenance dose should, therefore, be 30% less than the Prograf or Advagraf dose.

In stable patients converted from tacrolimus immediate-release products (twice daily) to Envarsus (once daily) on a 1:0.7 (mg:mg) total daily dose basis, the mean systemic exposure to tacrolimus (AUC_{0-24}) was similar to that of immediate-release tacrolimus. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for Envarsus is similar to that of immediate-release tacrolimus. No studies have been conducted with conversion of patients from Advagraf to Envarsus; however, data from healthy volunteers would suggest that the same conversion rate is applicable as with the conversion from Prograf to Envarsus.

When converting from tacrolimus immediate-release products (e.g., Prograf capsules) or from Advagraf prolonged-release capsules to Envarsus, trough levels should be measured prior to conversion and within two weeks after conversion. Dose adjustments should be made to ensure that similar systemic exposure is maintained after the switch. It should be noted that black patients may require a higher dose to achieve the targeted trough levels.

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. Tacrolimus 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 to 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 Envarsus may need to be reduced.

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

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 and systemic exposure (AUC_{0-24}) is well correlated and is similar between the immediate-release formulation and Envarsus.

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 Envarsus, just prior to the next dose. Blood trough levels of tacrolimus should also be closely monitored following conversion from tacrolimus products, 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 Envarsus 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 of 5-20 ng/mL in kidney transplant patients in the early post-transplant period, and 5-15 ng/mL during subsequent maintenance therapy.

Special populations

Elderly patients (> 65 years)
There is no evidence currently available to indicate that dose should be adjusted in elderly patients.

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. In clinical studies patients converted from twice daily Prograf were converted to Envarsus at 1:0.85 (mg:mg).

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

Paediatric population
The safety and efficacy of Envarsus in children below 18 years of age have not yet been established.
No data are available.

Method of administration

Envarsus is a once-a-day oral formulation of tacrolimus. It is recommended that the oral daily dose of Envarsus is administered once daily in the morning.
The tablets should be swallowed whole with fluid (preferably water) immediately following removal from the blister. Envarsus should generally be taken on an empty stomach to achieve maximal absorption (see section 5.2).
Patients should be advised not to swallow the desiccant.

4.3 Contraindications

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

For prophylaxis of transplant rejection in adult heart, lung, pancreas, or intestine allograft recipients clinical data are not yet available for Envarsus.

During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

Substances with potential for interaction

Inhibitors or inducers of CYP3A4 should only be co-administered with tacrolimus after consulting a transplant specialist, due to the potential for drug interactions resulting in serious adverse reactions including rejection or toxicity (see section 4.5).

CYP3A4 inhibitors
Concomitant use with CYP3A4 inhibitors may increase tacrolimus blood levels, which could lead to serious adverse reactions, including nephrotoxicity, neurotoxicity and QT prolongation. It is recommended that concomitant use of strong CYP3A4 inhibitors (such as ritonavir, cobicistat, ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin or josamycin) with tacrolimus should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of coadministration, under the supervision of a transplant specialist, to adjust the tacrolimus dose if appropriate in order to maintain similar tacrolimus exposure. Renal function, ECG including the QT interval, and the clinical condition of the patient should also be closely monitored.
Dose adjustment needs to be based upon the individual situation of each patient. An immediate dose reduction at the time of treatment initiation may be required (see section 4.5).

Similarly, discontinuation of CYP3A4 inhibitors may affect the rate of metabolism of tacrolimus, thereby leading to subtherapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

CYP3A4 inducers
Concomitant use with CYP3A4 inducers may decrease tacrolimus blood levels, potentially increasing the risk of transplant rejection. It is recommended that concomitant use of strong CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine) with tacrolimus should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of coadministration, under the supervision of a transplant specialist, to adjust the tacrolimus dose if appropriate, in order to maintain similar tacrolimus exposure. Graft function should also be closely monitored (see section 4.5).
Similarly, discontinuation of CYP3A4 inducers may affect the rate of metabolism of tacrolimus, thereby leading to supratherapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

P-glycoprotein
Caution should be observed when co-administering tacrolimus with drugs that inhibit P-glycoprotein, as an increase in tacrolimus levels may occur. Tacrolimus whole

blood levels and the clinical condition of the patient should be monitored closely. An adjustment of the tacrolimus dose may be required (see section 4.5).

Herbal preparations

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

Other interactions

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 neurotoxic effects may increase the risk of these effects (see section 4.5).

Vaccination

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

Nephrotoxicity

Tacrolimus can result in renal function impairment in post-transplant patients. Acute renal impairment without active intervention may progress to chronic renal impairment. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. The risk for nephrotoxicity may increase when tacrolimus is concomitantly administered with drugs associated with nephrotoxicity (see section 4.5). Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, tacrolimus trough blood level and renal function should be monitored closely and dosage reduction should be considered if nephrotoxicity occurs.

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.

Eye disorders

Eye disorders, sometimes progressing to loss of vision, have been reported in patients treated with tacrolimus. Some cases have reported resolution on switching to alternative immunosuppression. Patients should be advised to report changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, and in such cases, prompt evaluation is recommended with referral to an ophthalmologist as appropriate.

Thrombotic microangiopathy (TMA) (including thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS))

The diagnosis of TMA, including thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. If TMA is diagnosed, prompt treatment is required, and discontinuation of tacrolimus should be considered at the discretion of the treating physician.
The concomitant administration of tacrolimus with a mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus, everolimus) may increase the risk of thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome).

Cardiac disorders

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed in tacrolimus treated patients on rare occasions. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload and oedema. Accordingly, high-risk patients 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 tacrolimus or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing *Torsades de pointes*. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.

Lymphoproliferative disorders and malignancies

Patients treated with tacrolimus have been reported to develop Epstein-Barr Virus (EBV)-associated lymphoproliferative disorders and other malignancies, including skin cancers and Kaposi's sarcoma (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 Envarsus. During treatment, careful monitoring with EBV-PCR (Polymerase-Chain-Reaction) is recommended. Positive EBV-PCR may persist for months and is *per se* not indicative of lymphoproliferative disease or lymphoma.

Kaposi's sarcoma, including cases with aggressive forms of disease and fatal outcomes, has been reported in patients receiving tacrolimus. In some cases, regression of Kaposi's sarcoma has been observed after reducing the intensity of immunosuppression.
As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown.

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.

Infection including opportunistic infections

Patients treated with immunosuppressants, including Envarsus, are at increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal) such as CMV infection, BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). Patients are also at an increased risk of infections with viral hepatitis (e.g., hepatitis B and C reactivation and *de novo* infection, as well as hepatitis E, which may become chronic). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions including graft rejection that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms. Prevention and management should be in accordance with appropriate clinical guidance.

Posterior reversible encephalopathy syndrome (PRES)

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 medicinal product 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

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

4.5 Interaction with other medicinal products and other forms of interaction

Metabolic interactions

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

Pharmacokinetics studies have indicated that the increase in tacrolimus blood levels when co-administered with inhibitors of CYP3A4 is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

It is recommended strongly to closely monitor tacrolimus blood levels under supervision of a transplant specialist, as well as monitor for graft function, QT prolongation (with ECG), renal function and other undesirable effects including neurotoxicity, whenever substances which have the potential to alter CYP3A4 metabolism are used concomitantly, and to adjust or interrupt the tacrolimus dose if appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4). Similarly, patients should be closely monitored when using tacrolimus concomitantly with multiple substances that affect CYP3A4 as the effects on tacrolimus exposure may be enhanced or counteracted.

Medicinal products which have effects on tacrolimus are listed in the table below. The examples of drug-drug interactions are not intended to be inclusive or comprehensive and therefore the label of each drug that is co-administered with tacrolimus should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Medicinal products which have effects on tacrolimus

Drug/Substance Class or Name	**Drug interaction effect**	**Recommendations concerning co-administration**
Grapefruit or grapefruit juice	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see section 4.4]*.	Avoid grapefruit or grapefruit juice.
Ciclosporin	May increase tacrolimus whole blood trough concentrations. In addition, synergistic/additive nephrotoxic effects can occur.	The simultaneous use of ciclosporin and tacrolimus should be avoided *[see section 4.4]*.
Products known to have nephrotoxic or neurotoxic effects: aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole + trimethoprim, NSAIDs, ganciclovir, acyclovir, amphotericin B, ibuprofen, cidofovir, foscarnet	May enhance nephrotoxic or neurotoxic effects of tacrolimus.	Concurrent use of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects should be avoided. When co-administration cannot be avoided, monitor renal function and other side effects and adjust tacrolimus dose if needed.

Drug/Substance Class or Name	**Drug interaction effect**	**Recommendations concerning co-administration**
Strong CYP3A4 inhibitors: antifungal agents (e.g., ketoconazole, itraconazole, posaconazole, voriconazole), the macrolide antibiotics (e.g., telithromycin, troleandomycin, clarithromycin, josamycin), HIV protease inhibitors (e.g., ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g., telaprevir, boceprevir, and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir), nefazodone, the pharmacokinetic enhancer cobicistat, and the kinase inhibitors idelalisib, ceritinib Strong interactions have also been observed with the macrolide antibiotic erythromycin	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., nephrotoxicity, neurotoxicity, QT prolongation) which requires close monitoring *[see section 4.4]*. Rapid and sharp increases in tacrolimus levels may occur, as early as within 1-3 days after co-administration, despite immediate reduction of tacrolimus dose. Overall tacrolimus exposure may increase >5 fold. When ritonavir combinations are co-administered, tacrolimus exposure may increase >50 fold. Nearly all patients may require a reduction in tacrolimus dose and temporary interruption of tacrolimus may also be necessary. The effect on tacrolimus blood concentrations may remain for several days after co-administration is completed.	It is recommended that concomitant use should be avoided. If co-administration of a strong CYP3A4 inhibitor is unavoidable, consider omitting the dose of tacrolimus the day the strong CYP3A4 inhibitor is initiated. Reinitiate tacrolimus the next day at a reduced dose based on tacrolimus blood concentrations. Changes in both tacrolimus dose and/or dosing frequency should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inhibitor. Upon completion, appropriate dose and dosing frequency of tacrolimus should be guided by tacrolimus blood concentrations. Monitor renal function, ECG for QT prolongation, and other side effects closely.

Drug/Substance Class or Name	**Drug interaction effect**	**Recommendations concerning co-administration**
Moderate or weak CYP3A4 inhibitors: antifungal agents (e.g., fluconazole, isavuconazole, clotrimazole, miconazole), the macrolide antibiotics (e.g., azithromycin), calcium channel blockers (e.g., nifedipine, nicardipine, diltiazem, verapamil), amiodarone, danazol, ethinylestradiol, lansoprazole, omeprazole, the HCV antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, the CMV antiviral letermovir, and the tyrosine kinase inhibitors nilotinib, crizotinib and imatinib and (Chinese) herbal preparations containing extracts of *Schisandra sphenanthera*	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see section 4.4]*. A rapid increase in tacrolimus level may occur.	Monitor tacrolimus whole blood trough concentrations frequently, starting within the first few days of co-administration. Reduce tacrolimus dose if needed *[see section 4.2]*. Monitor renal function, ECG for QT prolongation, and other side effects closely.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed *[see section 4.2]*. Monitor renal function, ECG for QT prolongation, and other side effects closely.
Strong CYP3A4 inducers: rifampicin, phenytoin, carbamazepine, apalutamide, enzalutamide, mitotane, or St. John's wort (*Hypericum perforatum*)	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see section 4.4]*. Maximal effect on tacrolimus blood concentrations may be achieved 1-2 weeks after coadministration. The effect may remain 1-2 weeks after completion of the treatment.	It is recommended that concomitant use should be avoided. If unavoidable, patients may require an increase in tacrolimus dose. Changes in tacrolimus dose should be individualized and adjusted as needed based on tacrolimus trough concentrations, which

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
		should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inducer. After use of the CYP3A4 inducer has ended, tacrolimus dose may need to be adjusted gradually. Monitor graft function closely.
Moderate CYP3A4 inducers: metamizole, phenobarbital, isoniazid, rifabutin, efavirenz, etravirine, nevirapine Weak CYP3A4 inducers: flucloxacillin	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed *[see section 4.2]*. Monitor graft function closely.
Caspofungin	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection. Mechanism of interaction has not been confirmed.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed *[see section 4.2]*. Monitor graft function closely.
Products known to have high affinity for plasma proteins, e.g.: NSAIDs, oral anticoagulants, oral antidiabetics	Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed *[see section 4.2]*.
Prokinetic agents: metoclopramide, cisapride, cimetidine, and magnesium-aluminium-hydroxide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation).	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed *[see section 4.2]*. Monitor closely for renal function, for QT prolongation with ECG, and for other side effects.

Drug/Substance Class or Name	**Drug interaction effect**	**Recommendations concerning co-administration**
Maintenance doses of corticosteroids	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed *[see section 4.2]*. Monitor graft function closely.
High dose prednisolone or methylprednisolone	May have impact on tacrolimus blood levels (increase or decrease) when administered for the treatment of acute rejection.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed.
Direct-acting antiviral (DAA) therapy	May have impact on the pharmacokinetics of tacrolimus by changes in liver function during DAA therapy, related to clearance of hepatitis virus. A decrease in tacrolimus blood levels may occur. However, the CYP3A4 inhibiting potential of some DAAs may counteract that effect or lead to increased tacrolimus blood levels.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed to ensure continued efficacy and safety.
Cannabidiol (P-gp inhibitor)	There have been reports of increased tacrolimus blood levels during concomitant use of tacrolimus with cannabidiol. This may be due to inhibition of intestinal P-glycoprotein, leading to increased bioavailability of tacrolimus.	Tacrolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor tacrolimus whole blood trough concentrations and adjust the tacrolimus dose if needed *[see sections 4.2 and 4.4]*.

Concomitant administration of tacrolimus with a mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus, everolimus) may increase the risk of thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (see section 4.4).

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). Care should be taken when tacrolimus is coadministered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Close monitoring of serum potassium is recommended.

Effect of tacrolimus on the metabolism of other 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.

Mycophenolic acid
Caution should be exercised when switching combination therapy from ciclosporin, which interferes with enterohepatic recirculation of mycophenolic acid, to tacrolimus, which is devoid of this effect, as this might result in changes of mycophenolic acid exposure. Drugs which interfere with mycophenolic acid's enterohepatic cycle have potential to reduce the plasma level and efficacy of mycophenolic acid. Therapeutic drug monitoring of mycophenolic acid may be appropriate when switching from ciclosporin to tacrolimus or *vice versa*.

Other interactions leading to clinically detrimental effects

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).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from women show that tacrolimus crosses the placenta. There is a risk for hyperkalaemia in the newborn (e.g. incidence in neonates of 7.2%, i.e., 8 of 111) which tends to normalise spontaneously. 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 potential adverse events of tacrolimus is recommended (in particular, effects on the kidneys).

Results from a non-interventional post-authorisation safety study [EUPAS37025]
A post-authorisation safety study analysed 2,905 pregnancies from the Transplant Pregnancy Registry International (TPRI), assessing outcomes in women treated with tacrolimus (383 reported prospectively, including 247 kidney and 136 liver transplant patients), and those on other immunosuppressants. Based on limited data (289 prospectively-reported pregnancies with 1st trimester tacrolimus exposure), study results did not indicate an increased risk of major malformations. A higher prevalence of spontaneous abortion was observed among women treated with tacrolimus compared with alternative immunosuppressants. Among kidney transplant patients there was also a higher prevalence of pre-eclampsia in women treated with tacrolimus. However, overall, there were insufficient evidence to conclude on the risk of these outcomes. Among kidney and liver transplant patients exposed to tacrolimus, 45% - 55% of their live births were premature, with 75% - 85% having a normal birth weight for gestational age. Similar results were observed for other immunosuppressants, although conclusions were hindered by limited evidence.

In rats and rabbits, tacrolimus caused embryofoetal 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 Envarsus.

Fertility

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

4.7 Effects on ability to drive and use machines

Envarsus may have a minor influence on the ability to drive and use machines. Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Envarsus is administered in association with alcohol.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions for tacrolimus (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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥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

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

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders, skin malignancies and Kaposi's sarcoma have been reported in association with tacrolimus treatment.

Immune system disorders

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

System Organ Class	**Frequency of adverse reactions**					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders		anaemia, thrombocyto-penia, leukopenia, red blood cell analyses abnormal, leukocytosis	coagulo-pathies, pancytopenia, neutropenia, coagulation and bleeding analyses, abnormal, thrombotic microangio-pathy	thrombotic thrombo-cytopenic purpura, hypopro-thrombin-aemia		pure red cell aplasia, agranulo-cytosis, haemolytic anaemia, febrile neutropeni a
Endocrine disorders				hirsutism		

System Organ Class	**Frequency of adverse reactions**					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Metabolism and nutrition disorders	diabetes mellitus, hyper-glycaemic conditions, hyper-kalaemia	anorexia, metabolic acidoses, other electrolyte ab-normalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnes-aemia, hypo-kalaemia, hypocalcemia, appetite decreased, hypercholest-erolaemia, hyperlipidaemia, hypertriglycerid-aemia, hypophos-phateaemia	dehydration, hypo-glycaemia, hypoprotein-aemia, hyperphos-phataemia			
Psychiatric disorders	insomnia	confusion and dis-orientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare	psychotic disorder			
Nervous system disorders	headache, tremor	nervous system disorders, seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dysaesthesias, writing impaired	encephalo-pathy, central nervous system haemorrhages and cerebrovas-cular accidents, coma, speech and language ab-normalities, paralysis and paresis, amnesia	hypertonia	myasthenia	Posterior reversible encephalo-pathy syndrome (PRES)
Eye disorders		eye disorders, vision blurred, photophobia	cataract	blindness		optic neuropathy

System Organ Class	**Frequency of adverse reactions**					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Ear and labyrinth disorders		tinnitus	hypoacusis	deafness neurosensory	hearing impaired	
Cardiac disorders		ischaemic coronary artery disorders, tachycardia	heart failures, ventricular arrhythmias and cardiac arrest, supraventri-cular arrhythmias, cardiomyo-pathies, ventricular hypertrophy, palpitations	pericardial effusion	Torsades de pointes	
Vascular disorders	hypertension	thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders	venous thrombosis deep limb, shock, infarction			
Respiratory, thoracic and mediastinal disorders		parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations	respiratory failures, respiratory tract disorders, asthma	acute respiratory distress syndrome		
Gastrointestinal disorders	diarrhoea, nausea	gastrointestinal signs and symptoms, vomiting, gastro-intestinal and abdominal pains, gastrointestinal inflammatory conditions, gastro-intestinal haem-orrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and distension, loose stools	acute and chronic pancreatitis, peritonitis, ileus paralytic, gastrooeso-phageal reflux disease, impaired gastric emptying	pancreatic pseudocyst, subileus		

System Organ Class	**Frequency of adverse reactions**					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Hepatobiliary disorders		bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice		veno-occlusive liver disease, hepatic artery thrombosis	hepatic failure	
Skin and subcutaneous tissue disorders		rash, pruritus, alopecias, acne, sweating increased	dermatitis, photo-sensitivity	toxic epidermal necrolysis (Lyell's syndrome)	Stevens-Johnson syndrome	
Musculoskeletal and connective tissue disorders		arthralgia, back pain, muscle cramps, pain in limb	joint disorders	mobility decreased		
Renal and urinary disorders	renal impairment	renal failure, renal failure acute, nephropathy toxic, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms	haemolytic uraemic syndrome, anuria		nephropathy, cystitis haem-orrhagic	
Reproductive system and breast disorders			dysmenorrhoea and uterine bleeding			
General disorders and administration site conditions		febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed	influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance	fall, ulcer, chest tightness, thirst	fat tissue increased	
Investigations	liver function tests abnormal	blood alkaline phosphatase increased, weight increased	amylase increased, ECG abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased		echo-cardiogram abnormal,	
Injury, poisoning and procedural complications		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.

In clinical studies in kidney transplant patients receiving Envarsus, the most frequent adverse reactions (at least in 2% of patients) were tremor, diabetes mellitus, blood creatinine increased, urinary tract infection, hypertension, BK virus infection, renal impairment, diarrhoea, toxicity to various agents, and toxic nephropathy all of which are known to occur in the respective patient population under immunosuppressive treatment. In all, there appears to be no significant difference in the pattern of adverse events suspected to be causally related to study drug between once daily Envarsus and tacrolimus immediate-release capsules (Prograf).
Among the most frequent adverse reactions (at least in 2% of patients) in clinical studies in liver transplant patients receiving Envarsus were tremor, headache, fatigue, hyperkalaemia, hypertension, renal failure, blood creatinine increased, dizziness, hepatitis C, muscle spasms, tinea infection, leukopenia, sinusitis, and upper respiratory tract infections (URTI), all of which are known to occur in the respective patient population under immunosuppressive treatment. As in kidney transplant recipients, there appears to be no meaningful difference in the pattern of suspected adverse drug reactions between once daily Envarsus and tacrolimus immediate-release capsules (Prograf).
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:
Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.
It should be noted however, that there has been no direct experience with Envarsus in overdose.

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.

Pharmacodynamic effects

Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both *in vitro* and *in vivo* experiments.
In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.

Clinical efficacy and safety

Results from clinical studies performed with once-daily tacrolimus

Kidney transplantation
The efficacy and safety of Envarsus and Prograf, both in combination with mycophenolate mofetil (MMF), corticosteroids and IL-2 receptor antagonist as per the standard of care were compared in a randomised, double-blind, double-dummy study, in 543 *de novo* kidney transplant recipients.
The percentage of patients with one or greater than one episode of clinically-suspected and treated rejections during the 360-day study was 13.8% for the Envarsus group (N=268) and 15.6% for the Prograf group (N=275). The event rate for centrally read, biopsy-confirmed acute rejection (BPAR) during the 360-day study was 13.1% in the Envarsus group (N=268) and 13.5% in the Prograf group (N=275). The efficacy failure rate as measured by the composite endpoint of death, graft loss, centrally read BPAR and loss to follow-up was 18.3% in the Envarsus group and 19.6% in the Prograf group. The treatment difference (Envarsus-Prograf) was -1.35% (95% confidence interval [-7.94%, 5.27%]). Treatment-emergent fatal adverse events occurred in 1.8% of Envarsus patients and 2.5% of Prograf patients.

The efficacy and safety of Envarsus and Prograf, both in combination with mycophenolate mofetil (MMF) or mycophenolate sodium (MPS) and corticosteroids, were compared in 324 stable kidney transplant recipients. The event rate for locally read BPAR during the 360-day study was 1.2% in the Envarsus group (N=162) post conversion from Prograf at a dose ratio of 1:0.7 (mg:mg) and 1.2% in the group maintained on Prograf (N=162). The efficacy failure rate as measured by the composite endpoint of death, graft loss, locally read BPAR and loss to follow-up was 2.5% in both the Envarsus and Prograf groups. The treatment difference (Envarsus-Prograf) was 0% (95% confidence interval [-4.21%, 4.21%]). The treatment failure rate using the same composite end-point with centrally read BPAR was 1.9% in the Envarsus group and 3.7% in the Prograf group (95% confidence interval [-6.51%, 2.31%]). Treatment emergent fatal adverse events occurred in 1.2% of Envarsus patients and 0.6% of Prograf patients.

Liver transplantation

The pharmacokinetics, efficacy and safety of Envarsus and tacrolimus immediate-release capsules, both in combination with corticosteroids were compared in 117 liver transplant recipients, of whom 88 received treatment with Envarsus. In the *de novo* liver transplant study, 29 subjects were treated with Envarsus. The event rate of biopsy-confirmed acute rejection within the 360-day study period was not significantly different between the Envarsus group and the tacrolimus immediate-release group. The overall incidence of fatal treatment emergent adverse events for the combined *de novo* and stable liver transplant population was not significantly different between the Envarsus group and the tacrolimus immediate-release group.

5.2 Pharmacokinetic properties

Absorption

The oral bioavailability of Envarsus was decreased when the medicinal product was administered after a meal; the extent of absorption was decreased by 55% and the maximum plasma concentration was decreased by 22% when taken directly after a high-fat meal. Therefore, Envarsus should generally be taken on an empty stomach to achieve maximal absorption.

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed. Envarsus 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 6 hours (t_{max}) at steady state.

Absorption is variable and the mean oral bioavailability of tacrolimus is in the range of 20%-25% (individual range in adult patients 6%-43%). The oral bioavailability is approximately 40% higher for Envarsus as compared to the same dose of tacrolimus immediate-release formulation (Prograf) in kidney transplant patients.

Higher C_{avg} (~50%), reduced peak trough fluctuation (C_{max}/C_{min}) and a longer T_{max} were seen for Envarsus when compared with both, tacrolimus immediate-release formulation (Prograf)

and a tacrolimus once daily formulation (Advagraf). Mean values for C_{max}, percentage degree of fluctuation and percentage degree of swing were significantly lower with administration of Envarsus tablets.

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

In vitro test results indicate that there is no risk of *in vivo* dose dumping related to alcohol intake.

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 1 300 L (healthy subjects). Corresponding data based on whole blood averaged 47.6 L.

Biotransformation

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5). 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.

Elimination

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 30 hours.
Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the

urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination bile being the principal route of elimination.

5.3 Preclinical safety data

The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus. Embryofoetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic 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 count and motility was observed in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Lactose monohydrate
Macrogol 6000
Poloxamer 188
Magnesium stearate
Tartaric acid (E334)
Butylated hydroxytoluene (E321)
Dimethicone 350

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

After opening the aluminium foil wrapper: 45 days.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original aluminium foil wrapper in order to protect from light.

6.5 Nature and contents of container

PVC/alu blisters containing 10 prolonged-release tablets. 3 blisters are packed together in an aluminium foil wrapper containing a desiccant.

Pack sizes of 30, 60 and 90 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Chiesi Limited
333 Styal Road
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M22 5LG
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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 08829/0185

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/03/2025