

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Envarsus 0.75 mg prolonged-release tablets
Envarsus 1 mg prolonged-release tablets
Envarsus 4 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Envarsus 0.75 mg prolonged-release tablets

Each prolonged-release tablet contains 0.75 mg tacrolimus (as monohydrate).

Excipient with known effect:

Each tablet contains 41.7 mg lactose (as monohydrate).

Envarsus 1 mg prolonged-release tablets

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

Excipient with known effect:

Each tablet contains 41.7 mg lactose (as monohydrate).

Envarsus 4 mg prolonged-release tablets

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

Excipient with known effect:

Each tablet contains 104 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

0.75 mg:

Oval, white to off-white uncoated tablet, debossed with “0.75” on one side and “TCS” on the other side.

1 mg:

Oval, white to off-white uncoated tablet, debossed with “1” on one side and “TCS” on the other side.

4 mg:

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. Envarsus 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. Envarsus 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 Envarsus 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.

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

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. Envarsus should be administered in the morning.

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. Envarsus 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 Envarsus, 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

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.

Elderly patients (> 65 years)

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

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.

Patients should be advised not to swallow the desiccant. 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).

Envarsus is **not** interchangeable with other existing tacrolimus containing medicines (immediate release or prolonged release) on an equal dose by dose basis.

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.

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 or rifabutin), are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

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

The combined administration of 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 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 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 Envarsus 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 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 Envarsus. 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 Envarsus 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 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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric population

Envarsus is not recommended for use in children below 18 years of age due to the limited data on safety and/or efficacy

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 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 Hepatitis C Virus (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, nocardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole and nefazodone.

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

Lansoprazol 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: Interactions have been observed with rifampicin, phenytoin, and 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).

Paediatric population

Interaction studies have only been performed in adults

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 events 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 potential adverse events 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 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.

No studies on the effects of tacrolimus (Envarsus) 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 for tacrolimus (occurring in >10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia.

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.

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

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

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
<u>Blood and lymphatic system disorders</u>		anaemia, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leukocytosis	coagulopathies, pancytopenia, neutropenia, coagulation and bleeding analyses, abnormal	thrombotic thrombocytopenic purpura, hypoprotrombin-aemia		pure red cell aplasia, agranulocytosis, haemolytic anaemia
<u>Endocrine disorders</u>				hirsutism		
<u>Metabolism and nutrition disorders</u>	diabetes mellitus, hyperglycaemic conditions, hyperkalaemia	anorexia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypo-magnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia	dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia			

System Organ Class	Frequency of adverse reactions					
	Very common	Common	Uncommon	Rare	Very rare	Not known
<u>Psychiatric disorders</u>	insomnia	confusion and dis-orientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare	psychotic disorder			
<u>Nervous system disorders</u>	headache, tremor	nervous system disorders seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dysaesthesias, writing impaired	encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, speech and language abnormalities, paralysis and paresis, amnesia	hypertonia	myasthenia	
<u>Eye disorders</u>		eye disorders, vision blurred, photophobia	cataract	blindness		
<u>Ear and labyrinth disorders</u>		tinnitus	hypoacusis	deafness neurosensory	hearing impaired	
<u>Cardiac disorders</u>		ischaemic coronary artery disorders, tachycardia	heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ECG investigations abnormal, ventricular hypertrophy, palpitations, heart rate and pulse investigations abnormal	pericardial effusion	Echo-cardiogram abnormal	
<u>Vascular disorders</u>	hypertension	thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders	venous thrombosis deep limb, shock, infarction			

System Organ Class	Frequency of adverse reactions					
	Very common	Common	Uncommon	Rare	Very rare	Not known
<u>Respiratory, thoracic and mediastinal disorders</u>		parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations	respiratory failures, respiratory tract disorders, asthma	acute respiratory distress syndrome		
<u>Gastrointestinal disorders</u>	diarrhoea, nausea	gastro-intestinal signs and symptoms, vomiting, gastro-intestinal and abdominal pains, gastro-intestinal inflammatory conditions, gastro-intestinal haemorrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and distension, loose stools	acute and chronic pancreatitis, peritonitis, blood amylase increased, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying	pancreatic pseudocyst, subileus		
<u>Hepatobiliary disorders</u>	liver function tests abnormal	bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice		veno-occlusive liver disease, hepatic artery thrombosis	hepatic failure	
<u>Skin and subcutaneous tissue disorders</u>		rash, pruritus, alopecias, acne, sweating increased	dermatitis, photo-sensitivity	toxic epidermal necrolysis (Lyell's syndrome)	Stevens Johnson syndrome	
<u>Musculoskeletal and connective tissue disorders</u>		arthralgia, back pain, muscle cramps, pain in limb	joint disorders			
<u>Renal and urinary disorders</u>	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 haemorrhagic	

System Organ Class	Frequency of adverse reactions					
	Very common	Common	Uncommon	Rare	Very rare	Not known
<u>Reproductive system and breast disorders</u>			dysmenorrhoea and uterine bleeding			
<u>General disorders and administration site conditions</u>		febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed, blood alkaline phosphatase increased, weight increased	weight decreased, influenza like illness, blood lactate dehydrogenase increased, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance	fall, ulcer, chest tightness, mobility decreased, thirst	fat tissue increased	
<u>Injury, poisoning and procedural complications</u>		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 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 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.

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 effect

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 trials performed with once-daily tacrolimus, Envarsus

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 was 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 episodes 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 BPAP 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, was compared in 324 stable kidney transplant recipients. The event rate for locally read biopsy-confirmed acute rejection (BPAP) 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 was 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 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. 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 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. 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 blisters containing 10 prolonged-release tablets. 3 blisters are packed together in an aluminium foil wrapper containing a desiccant.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER(S)

0,75mg	1mg	4mg
EU/1/14/935/001	EU/1/14/935/004	EU/1/14/935/007
EU/1/14/935/002	EU/1/14/935/005	EU/1/14/935/008
EU/1/14/935/003	EU/1/14/935/006	EU/1/14/935/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18.07.2014

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. MANUFACTURER 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. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Chiesi Farmaceutici S.p.A.

Via San Leonardo 96
43122 Parma
Italy

Rottendorf Pharma GmbH

Ostenfelder Strasse 51-61
D-59320 Ennigerloh
Germany

Chiesi Pharmaceuticals GmbH

Gonzagagasse 16/16
1010 Vienna, Austria

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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State, the Marketing Authorisation Holder MAH shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder should ensure that, at launch, all Healthcare Professionals who are expected to prescribe or dispense Envarsus are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Educational material for Healthcare Professionals
- Patient cards to be given to patients with the product

The educational material for Healthcare Professionals should include information on the following key elements:

- The authorised indications
- The need for prescribing and dispensing with attention to pharmaceutical form (prolonged release) and posology (once daily administration).
- The importance of avoiding inadvertent switching between tacrolimus containing products and the risk of under and overdosing if monitoring is inadequate.
- The clinical risks associated with over- and under-dosing.
- The need for specialist supervision and monitoring if there is a clinical decision to switch a patient to another tacrolimus containing products.
- The role of the patient card in ensuring that patients are aware of the product they are taking and the recommendations for safe and effective use in particular once daily dose and the importance of avoiding switching between other tacrolimus containing products except under the advice and supervision of your doctor

The patient card should include information on the following key elements :

- The product name
- That the dose is once daily
- The importance of avoiding switching between other tacrolimus containing products except under the advice and supervision of physicians.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Envarsus 0.75 mg prolonged-release tablets
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 0.75 mg tacrolimus (as monohydrate).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information'.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
60 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 prolonged-release tablets within 45 days of opening the aluminium wrapping.

9. SPECIAL STORAGE CONDITIONS

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

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

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/935/001
EU/1/14/935/002
EU/1/14/935/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Envarsus 0.75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Envarsus 1 mg prolonged-release tablets
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information'.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
60 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 prolonged-release tablets within 45 days of opening the aluminium wrapping.

9. SPECIAL STORAGE CONDITIONS

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

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

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/935/004
EU/1/14/935/005
EU/1/14/935/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Envarsus 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Envarsus 4 mg prolonged-release tablets
Tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information'.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
60 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 prolonged-release tablets within 45 days of opening the aluminium wrapping.

9. SPECIAL STORAGE CONDITIONS

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

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

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/935/007
EU/1/14/935/008
EU/1/14/935/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Envarsus 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER**

1. NAME OF THE MEDICINAL PRODUCT

Envarsus 0.75 mg prolonged-release tablets
Tacrolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Chiesi

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Once daily

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER**

1. NAME OF THE MEDICINAL PRODUCT

Envarsus 1 mg prolonged-release tablets
Tacrolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Chiesi

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Once daily

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER**

1. NAME OF THE MEDICINAL PRODUCT

Envarsus 4 mg prolonged-release tablets
Tacrolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Chiesi

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Once daily

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM FOIL WRAPPER

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

Envarsus 0.75 mg prolonged-release tablets
Tacrolimus
For oral use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 tablets

6. OTHER

Use all the prolonged-release tablets within 45 days of opening the aluminium wrapping.
Store in the original aluminium foil wrapper in order to protect from light.
Once daily.

Chiesi

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM FOIL WRAPPER

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

Envarsus 1 mg prolonged-release tablets
Tacrolimus
For oral use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 tablets

6. OTHER

Use all the prolonged-release tablets within 45 days of opening the aluminium wrapping.
Store in the original aluminium foil wrapper in order to protect from light.
Once daily.

Chiesi

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM FOIL WRAPPER

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

Envarsus 4 mg prolonged-release tablets
Tacrolimus
For oral use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 tablets

6. OTHER

Use all the prolonged-release tablets within 45 days of opening the aluminium wrapping.
Store in the original aluminium foil wrapper in order to protect from light.
Once daily.

Chiesi

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Envarsus 0.75 mg prolonged-release tablets

Envarsus 1 mg prolonged-release tablets

Envarsus 4 mg prolonged-release tablets

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

1. What Envarsus is and what it is used for

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

You may also be given Envarsus 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.

Envarsus is used in adults.

2. What you need to know before you take Envarsus

Do not take Envarsus:

- if you are allergic to tacrolimus or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to sirolimus or to any macrolide-antibiotic (e.g. erythromycin, clarithromycin, josamycin).

Warnings and precautions

Envarsus contains the active substance tacrolimus presented in a prolonged release formulation. Envarsus is taken once daily and is **not** interchangeable with other existing medicines containing tacrolimus (immediate release or prolonged release) on an equal dose by dose basis.

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

- if you have, or have had, liver problems.

- if you have diarrhoea for more than one day.

Your doctor may need to adjust your dose of Envarsus.

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

You should limit your exposure to the sun and UV (ultraviolet) light whilst taking Envarsus. 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 Envarsus is not recommended in children and adolescents under 18 years.

Other medicines and Envarsus

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

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

Envarsus blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Envarsus, which may require interruption, an increase or a decrease in Envarsus 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 substances (e.g. 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
- prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression
- herbal preparations containing St. John’s Wort (*Hypericum perforatum*)

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

While you take Envarsus 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), nonsteroidal anti-inflammatory substances (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes.

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

Envarsus with food and drink

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

Pregnancy and breast-feeding

Tacrolimus crosses the placenta. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Tacrolimus passes into breast milk. Therefore, you should not breast-feed whilst taking Envarsus.

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

Envarsus contains lactose

Envarsus 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.

3. How to take Envarsus

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

This medicine should only be prescribed for 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:

0.11 - 0.17 mg per kg body weight per day

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

Your dose depends on your general condition and on which other immunosuppressive medicines you are taking. Following the initiation of your treatment with this medicine, 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 Envarsus dose once your condition has stabilised.

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

Envarsus is taken orally once daily, generally on an empty stomach.

Take the tablets immediately following removal from the blister. The tablets should be swallowed **whole** with a glass of water. Do not swallow the desiccant contained in the foil wrapper.

If you take more Envarsus than you should

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

If you forget to take Envarsus

Do not take a double dose to make up for a forgotten tablet. Take the tablet as soon as possible on the same day.

If you stop taking Envarsus

Stopping your treatment with Envarsus 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, this medicine can cause side effects, although not everybody gets them.

Tacrolimus 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 Envarsus. Please contact your doctor immediately, should you experience severe effects.

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

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 cramps
- insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- general weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling 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 contents 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

Unknown frequencies side effects (may affect less than 1 in 10,000 people):

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

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 Envarsus

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, blister and wrapper after 'EXP'. The expiry date refers to the last day of that month.

Do not store above 25°C.

Store in the original aluminium foil wrapper in order to protect from light.

Use all the prolonged-release tablets within 45 days of opening the aluminium wrapping.

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 Envarsus contains

- The active substance is tacrolimus.
Each prolonged-release tablet contains 0.75 mg tacrolimus (as monohydrate).
Each prolonged-release tablet contains 1.0 mg tacrolimus (as monohydrate).
Each prolonged-release tablet contains 4.0 mg tacrolimus (as monohydrate).
- The other excipients are hypromellose, lactose monohydrate, macrogol 6000, poloxamer 188, magnesium stearate, tartaric acid (E334), butylated hydroxytoluene (E321), dimethicone 350.

What Envarsus looks like and contents of the pack

Envarsus 0.75 mg prolonged-release tablets are oval, white to off-white uncoated tablet, debossed with “0.75” on one side and “TCS” on the other side.

Envarsus 1 mg prolonged-release tablets are oval, white to off-white uncoated tablet, debossed with “1” on one side and “TCS” on the other side

Envarsus 4 mg prolonged-release tablets are oval, white to off-white uncoated tablet, debossed with “4” on one side and “TCS” on the other side.

Envarsus is supplied in PVC blisters containing 10 tablets. 3 blisters are packed together within a protective aluminium foil wrapper, including a desiccant. Packs of 30, 60 and 90 prolonged-release tablets are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma

Manufacturer

Rottendorf Pharma GmbH
Ostenfelder Straße 51 - 61
59320 Ennigerloh
North Rhine-Westphalia
Germany

or

Chiesi Farmaceutici S.p.A.
Via San Leonardo 96
43122 Parma
Italy

or

Chiesi Pharmaceuticals GmbH
Gonzagasse 16/16
1010 Vienna
Austria

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Chiesi sa/nv
Tél/Tel: + 32 (0)2 788 42 00

България

Chiesi Bulgaria EOOD
Тел.: + 359 29201205

Česká republika

Chiesi CZ s.r.o.
Tel: +420 261221745

Danmark

Chiesi Pharma AB
Tlf: +46 8 753 35 20

Deutschland

Chiesi GmbH
Tel: + 49 40 89724-0

Eesti

Chiesi Pharmaceuticals GmbH
Tel: +43 1 4073919

Ελλάδα

Chiesi Hellas AEBE
Τηλ: + 30 210 6179763

España

Chiesi España, S.A.U.
Tel: + 34 93 494 8000

France

Chiesi S.A.S
Tél: + 33 1 47688899

Hrvatska

Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Ireland

Chiesi Ltd
Tel: + 44 0161 4885555

Ísland

Chiesi Pharma AB
Tlf: +46 8 753 35 20

Italia

Chiesi Farmaceutici S.p.A.
Tel: + 39 0521 2791

Lietuva

Chiesi Pharmaceuticals GmbH
Tel: +43 1 4073919

Luxembourg/Luxemburg

Chiesi sa/nv
Tél/Tel: + 32 (0)2 788 42 00

Magyarország

Chiesi Hungary Kft.
Tel.: +36-1-429 1060

Malta

Chiesi Farmaceutici S.p.A.
Tel: + 39 0521 2791

Nederland

Chiesi Pharmaceuticals B.V.
Tel: + + 31 0 88 5016400

Norge

Chiesi Pharma AB
Tlf: +46 8 753 35 20

Österreich

Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Polska

Chiesi Poland Sp. z.o.o.
Tel.: + 48 22 620 1421

Portugal

Chiesi Farmaceutici S.p.A.
Tel: + 39 0521 2791

România

Chiesi Romania S.R.L.
Tel: + 40 212023642

Slovenija

Chiesi Slovenija d.o.o.
Tel: + 386-1-43 00 901

Slovenská republika

Chiesi Slovakia s.r.o.
Tel: + 421 259300060

Suomi/Finland

Chiesi Pharma AB
Tlf: +46 8 753 35 20

Κύπρος

Chiesi Farmaceutici S.p.A.
Τηλ: + 39 0521 2791

Sverige

Chiesi Pharma AB
Tlf: +46 8 753 35 20

Latvija

Chiesi Pharmaceuticals GmbH
Tel: + + 43 1 4073919

United Kingdom

Chiesi Ltd
Tel: + 44 0161 4885555

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Other sources of information

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