SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dailiport 1 mg prolonged-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect
Each prolonged-release hard capsule contains 102 mg of lactose (as monohydrate).
Each prolonged-release hard capsule contains 7.4 microgram of Sunset yellow FCF (E110).
Each prolonged-release hard capsule contains 0.6 microgram of Allura red AC (E129).

The printing ink used to mark the capsule contains trace amounts of:
- Allura Red AC Aluminum Lake (E129) (14 %w/w of total printing ink composition);
- Sunset Yellow FCF Aluminum Lake (E110) (3%w/w of total printing ink composition);
- lecithin (soya) (0.99%w/w of total printing ink composition).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release hard capsule.

Gelatin capsule size 4 with a light brown body and a white cap, imprinted in black with “1 mg”, containing white to yellowish powder or compacted powder (length 14.0 – 14.6 mm).

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

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

Different oral formulations of tacrolimus should not be substituted without clinical supervision. Inadvertent, unintentional or unsupervised switching between different oral formulation of tacrolimus with different release characteristics is unsafe. This can lead to graft rejection or increased incidence of adverse reactions, including under- or overimmunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Posology
The recommended initial doses presented below are intended to act solely as a guideline. Dailiport 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. Dailiport dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

In *de novo* kidney and liver transplant patients AUC0-24 of tacrolimus for tacrolimus prolonged-release on Day 1 was 30% and 50% lower respectively, when compared with that for tacrolimus immediate-release at equivalent doses. By Day 4, systemic exposure as measured by trough levels is similar for both kidney and liver transplant patients with both formulations. Careful and frequent monitoring of tacrolimus trough levels is recommended in the first two weeks post-transplant with Dailiport to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, adjustments to the Dailiport dose regimen may take several days before steady state is achieved.

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

Prophylaxis of kidney transplant rejection
Dailiport therapy should commence at a dose of 0.20 - 0.30 mg/kg/day administered

once daily in the morning. Administration should commence within 24 hours after the completion of surgery.

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

Prophylaxis of liver transplant rejection
Dailiport therapy should commence at a dose of 0.10 - 0.20 mg/kg/day administered once daily in the morning. Administration should commence approximately 12-18 hours after the completion of surgery. Dailiport doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Dailiport monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Conversion of tacrolimus immediate-release-treated patients to Dailiport
Allograft transplant patients maintained on twice daily tacrolimus immediate-release dosing requiring conversion to once daily Dailiport should be converted on a 1:1 (mg:mg) total daily dose basis. Dailiport should be administered in the morning.

In stable patients converted from tacrolimus immediate-release (twice daily) to tacrolimus prolonged-release (once daily) on a 1:1 (mg:mg) total daily dose basis, the systemic exposure to tacrolimus (AUC0-24) for tacrolimus prolonged-release was approximately 10% lower than that for tacrolimus immediate-release. The relationship between tacrolimus trough levels (C24) and systemic exposure (AUC0-24) for tacrolimus prolonged-release is similar to that of tacrolimus immediate-release. When converting from tacrolimus immediate-release to Dailiport, trough levels should be measured prior to conversion and within two weeks after conversion. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made to maintain similar systemic exposure. Dose adjustments should be made to ensure that similar systemic exposure is maintained.

Conversion from ciclosporin to tacrolimus
Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy (see sections 4.4 and 4.5). The combined administration of ciclosporin and tacrolimus is not recommended. Dailiport therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12 - 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

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

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

Treatment of allograft rejection after heart transplantation
In adult patients converted to Dailiport, an initial oral dose of 0.15 mg/kg/day should be administered once daily in the morning.

Treatment of allograft rejection after transplantation of other allografts
Although there is no clinical experience with tacrolimus prolonged-release in lung-, pancreas- or intestine-transplanted patients, tacrolimus immediate-release have been used in lung-transplanted patients at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

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

As an aid to optimise dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood. Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. The relationship between tacrolimus trough levels (C24) and systemic exposure (AUC 0-24) is similar between tacrolimus prolonged-release and tacrolimus immediate-release capsules.

Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Tacrolimus blood trough levels should be determined approximately 24 hours post-dosing of Dailiport, just prior to the next dose. Frequent trough level monitoring in the initial two weeks post transplantation is recommended, followed by periodic monitoring during maintenance therapy. Blood trough levels of tacrolimus should also be closely monitored following conversion from tacrolimus immediate-release to Dailiport, 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 Dailiport dose regimen it may take several days before the targeted steady state is achieved.

Data from clinical studies suggest that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range 5 - 20 ng/ml in liver transplant recipients and 10 - 20 ng/ml in kidney and heart transplant patients in the early post-transplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5 - 15 ng/ml in liver, kidney and heart transplant recipients.

Special populations

Hepatic impairment

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

Renal impairment

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

Race

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

Gender

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

Elderly

There is no evidence currently available to indicate that dosing should be adjusted in older people.

Paediatric population

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

Method of administration

Dailiport is a once-a-day oral formulation of tacrolimus. It is recommended that the oral daily dose of Dailiport be administered once daily in the morning.

Dailiport prolonged-release hard capsules should be taken immediately following removal from the blister. Patients should be advised not to swallow the desiccant. The capsules should be swallowed ***whole*** with fluid (preferably water). Dailiport should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption (see section 5.2). A forgotten morning dose should be taken as soon as possible on the same day. A double dose should not be taken on the next morning.

In patients unable to take oral medicinal products during the immediate post-transplant period, tacrolimus therapy can be initiated intravenously at a dose approximately $1/5^{th}$ of the recommended oral dose for the corresponding indication. Therefore, i.v. tacrolimus formulations are available.

4.3 Contraindications

Hypersensitivity to the active substance, soya, peanut, or to any of the excipients

listed in section 6.1.
Hypersensitivity to other macrolides.

4.4 Special warnings and precautions for use

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

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

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

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

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 co-administration, 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 co-administration, 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*) or other herbal preparations should be avoided when taking Dailiport due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity (see section 4.5).

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 drugs known to have nephrotoxic or 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.

Gastrointestinal disorders
Gastrointestinal perforation has been reported in patients treated with tacrolimus. As

gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur.

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

Cardiac disorders

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed in patients treated with tacrolimus immediate-release on rare occasions and may also occur with Dailiport. 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 Dailiport, or change of treatment to another immunosuppressive agent should be considered.

Tacrolimus may prolong the QT interval and may cause *Torsades de Pointes*. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see section 4.5).

Lymphoproliferative disorders and malignancies

Patients treated with tacrolimus have been reported to develop Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders 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 Dailiport. 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.

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.

Infections including opportunistic infections
Patients treated with immunosuppressants, including Dailiport 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 (for example, 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 rejections that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating hepatic 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.

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 haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP))
The diagnosis of TMA, including thrombotic thrombocytopaenic 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 haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura).

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

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.

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

Dailiport contains lactose and azo colouring agents, containing sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains the azo colouring agents Sunset yellow FCF (E110) and Allura red AC (E129) which may cause allergic reactions.

This medicinal product contains less than 1 mmol sodium (23 mg) per prolonged-release hard capsules, that is to say essentially ‘sodium-free’.

The printing ink used to mark Dailiport capsules contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using Dailiport.

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 substances or herbal remedies 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 remedies 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 strongly recommended to closely monitor tacrolimus blood levels, under supervision of a transplant specialist, as well as, monitor for graft function as well as, QT prolongation (with ECG), renal function and other side effects including neurotoxicity, 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). 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 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.

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, posaconazole, voriconazole and isavuconazole the macrolide antibiotics such as erythromycin, telithromycin, troleandomycin.

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), or the CMV antiviral letermovir, the pharmacokinetic enhancer cobicistat, and the tyrosine kinase inhibitors idelalisib, ceritinib, nilotinib, crizotinib and imatinib. 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, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, HCV antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, nefazodone and (Chinese) herbal remedies containing extracts of *Schisandra sphenanthera*.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene,

lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethindrone, quinidine, tamoxifen, (triacetyl)oleandomycin, azithromycin.

Grapefruit juice has been reported to increase the blood level of tacrolimus and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) (see section 4.4) and should therefore be avoided.

Lansoprazole and ciclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations. In addition, synergistic/additive nephrotoxic effects can occur. The simultaneous use of ciclosporin and tacrolimus should be avoided (see section 4.4).

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.

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).

CYP3A4 inducers potentially leading to decreased tacrolimus blood levels
Clinically the following substances have been shown to decrease tacrolimus blood levels:
Strong interactions have been observed with rifampicin, phenytoin, apalutamide, enzalutamide, mitotane, 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, rifabutin, efavirenz, etravirine, nevirapine and isoniazid have the potential to decrease tacrolimus concentrations.

Co-administration of tacrolimus with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of tacrolimus with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and tacrolimus are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

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.

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.

Weak CYP3A4 inducers-Flucloxacillin
Co-administration 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.

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
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 (sulfamethoxazole + trimethoprim), NSAIDs, ganciclovir or aciclovir, cidofovir, foscarnet).

Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus. Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, monitor renal function and other side effects and adjust tacrolimus dose if needed.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse reactions on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In case of *in utero* exposure, monitoring of the newborn for the potential adverse 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 embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

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

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

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

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

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

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
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 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).

Undesirable effects

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Anaemia, Thrombocytopenia, Leukopenia, Re blood cell analyses abnormal, Leukocytosis
	Uncommon	Coagulopathies, Pancytopenia, Neutropenia Coagulation and bleeding analyses, abnorma Thrombotic microangiopathy
	Rare	Thrombotic thrombocytopenic purpura Hypoprothrombinaemia,
	Not known	Pure red cell aplasia, Agranulocytosis, haemolyti anaemia, febrile neutropenia
Endocrine disorders	Rare	Hirsutism
Metabolism and nutrition disorders	Very common	Diabetes mellitus, Hyperglycaemic condition Hyperkalaemia
	Common	Metabolic acidoses, Other electrolyte abnormalities Hyponatraemia, Fluid overload, Hyperuricaemia Hypomagnesaemia, Hypokalaemia Hypocalcaemia, Appetite decreased Hypercholesterolaemia, Hyperlipidaemia Hypertriglyceridaemia, Hypophosphataemia
	Uncommon	Dehydration, Hypoglycaemia, Hypoproteinaemia Hyperphosphataemia
Psychiatric disorders	Very common	Insomnia
	Common	Confusion and disorientation, Depression, Anxiet symptoms, Hallucination, Mental disorders, Depressed mood, Mood disorders an disturbances, Nightmare
	Uncommon	Psychotic disorder
Nervous system disorders	Very common	Headache, Tremor
	Common	Nervous system disorders seizures, Disturbances i consciousness, Peripheral neuropathies, Dizziness Paraesthesias and dysaesthesias, Writing impaired
	Uncommon	Encephalopathy, Central nervous syster haemorrhages and cerebrovascular accidents Coma, Speech and language abnormalities Paralysis and paresis, Amnesia

	Rare	Hypertonia
	Very rare	Myasthenia
	Not Known	Posterior reversible encephalopathy syndrom (PRES)
Eye disorders	Common	Eye disorders, Vision blurred, Photophobia
	Uncommon	Cataract
	Rare	Blindness
	Unknown	Optic neuropathy
Ear and labyrinth disorders	Common	Tinnitus
	Uncommon	Hypoacusis
	Rare	Deafness neurosensory
	Very rare	Hearing impaired
Cardiac disorders	Common	Ischaemic coronary artery disorders, Tachycardia
	Uncommon	Heart failures, Ventricular arrhythmias and cardia arrest, Supraventricular arrhythmias Cardiomyopathies, Ventricular hypertrophy Palpitations
	Rare	Pericardial effusion
	Very rare	*Torsades de Pointes*
Vascular disorders	Very common	Hypertension
	Common	Thromboembolic and ischaemic events, Vascula hypotensive disorders, Haemorrhage, Peripher vascular disorders
	Uncommon	Venous thrombosis deep limb, shock, infarction
Respiratory, thoracic and mediastinal disorders	Common	Parenchymal lung disorders, Dyspnoea, Pleura effusion, Cough, Pharyngitis, Nasal congestion an inflammations
	Uncommon	Respiratory failures, Respiratory tract disorders Asthma
	Rare	Acute respiratory distress syndrome
Gastrointestinal disorders	Very common	Diarrhoea, Nausea
	Common	Gastrointestinal signs and symptoms, Vomiting Gastrointestinal and abdominal pains Gastrointestinal inflammatory conditions Gastrointestinal haemorrhages, Gastrointestina ulceration and perforation, Ascites, Stomatitis an ulceration, Constipation, Dyspeptic signs an symptoms, Flatulence, Bloating and distension Loose stools
	Uncommon	Acute and chronic pancreatitis, Ileus paralytic Gastrooesophageal reflux disease, Impaired gastri emptying
	Rare	Pancreatic pseudocyst, subileus
Hepatobiliary disorders	Common	Bile duct disorders, Hepatocellular damage an hepatitis, Cholestasis and jaundice
	Rare	Venoocclusive liver disease, Hepatitic arter thrombosis
	Very rare	Hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash, pruritus, Alopecias, Acne, Sweating increase

	Uncommon	Dermatitis, Photosensitivity
	Rare	Toxic epidermal necrolysis (Lyell's syndrome)
	Very rare	Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Back pain, Muscle spasms, Pain i extremity
	Uncommon	Joint disorders
	Rare	Mobility decreased
Renal and urinary disorders	Very common	Renal impairment
	Common	Renal failure, Renal failure acute, Nephropath toxic, Renal tubular necrosis, Urinar abnormalities, Oliguria, Bladder and urethra symptoms
	Uncommon	Haemolytic uraemic syndrome, Anuria
	Very rare	Nephropathy, Cystitis haemorrhagic
Reproductive system and breast disorders	Uncommon	Dysmenorrhoea and uterine bleeding
General disorders and administration site conditions	Common	Febrile disorders, Pain and discomfort, Astheni conditions, Oedema, Body temperature perceptio disturbed
	Uncommon	Influenza like illness, Feeling jittery, Feelin abnormal, Multi-organ failure, Chest pressur sensation, Temperature intolerance
	Rare	Fall, Ulcer, Chest tightness, Thirst
	Very rare	Fat tissue increased
	Unknown	Febrile neutropenia
Investigations	Very common	Liver function tests abnormal
	Common	Blood alkaline phosphatase increased, weigh increased
	Uncommon	Amylase increased, ECG investigations abnorma Heart rate and pulse investigations abnorma Weight decreased, Blood lactate dehydrogenas increased
	Very rare	Echocardiogram abnormal, Electrocardiogram Q prolonged
Injury, poisoning and procedural complications	Common	Primary graft dysfunction

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

Description of selected adverse reactions

Pain in extremity has been described in a number of published case reports as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS). This typically presents as a bilateral and symmetrical, severe, ascending pain in the lower extremities and may be associated with supra-therapeutic levels of tacrolimus. The syndrome may respond to tacrolimus dose reduction. In some cases, it was necessary to switch to alternative immunosuppression.

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 Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in 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.

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 trials performed with once-daily tacrolimus

Liver transplantation

The efficacy and safety of tacrolimus prolonged-release and tacrolimus immediate-release, both in combination with corticosteroids, was compared in 471 *de novo* liver transplant recipients. The event rate of biopsy confirmed acute rejection within the first 24 weeks after transplantation was 32.6% in the tacrolimus prolonged-release group (N=237) and 29.3% in the tacrolimus immediate-release group (N=234). The treatment difference (prolonged-release – immediate-release) was 3.3% (95% confidence interval [-5.7%, 12.3%]).The 12-month patient survival rates were 89.2% for tacrolimus prolonged-release and 90.8% for tacrolimus immediate-release; in the tacrolimus prolonged-release arm 25 patients died (14 female, 11 male) and in the tacrolimus immediate-release arm 24 patients died (5 female, 19 male). 12-month graft survival was 85.3% for tacrolimus prolonged-release and 85.6% for tacrolimus immediate-release.

Kidney transplantation

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

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

was 96.7% for tacrolimus prolonged-release, 92.9% for tacrolimus immediate-release and 95.7% for ciclosporin.

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

In prospective studies tacrolimus immediate-release were investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of tacrolimus immediate-release in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus immediate-release were used as primary treatment in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarised below.

Lung transplantation

The interim analysis of a recent multicentre study using tacrolimus immediate-release discussed 110 patients who underwent 1:1 randomisation to either tacrolimus or ciclosporin. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus ciclosporin-treated patients (11.5% versus 22.6%) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86% versus 8.57%), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8% in the tacrolimus and 83% in the ciclosporin group.

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

In an additional two-centre study, 26 patients were randomised to the tacrolimus versus 24 patients to the ciclosporin group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml. The 1-year survival rates were 73.1% in the tacrolimus versus 79.2% in the ciclosporin group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7% versus 45.8%) and at 1 year after lung transplantation (50% versus 33.3%). The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

Pancreas transplantation

A multicentre study using tacrolimus immediate-release included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomised to tacrolimus (n = 103) or to ciclosporin (n = 102). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6. Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3% versus 74.5% with ciclosporin ($p < 0.0005$), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from ciclosporin to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy.

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

5.2 Pharmacokinetic properties

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

Absorption is variable and the mean oral bioavailability of tacrolimus (investigated with the tacrolimus immediate-release formulation) is in the range of 20% - 25% (individual range in adult patients 6% - 43%). The oral bioavailability of tacrolimus prolonged-release was reduced when it was administered after a meal. Both the rate and extent of absorption of tacrolimus prolonged-release were reduced when administered with food.

Bile flow does not influence the absorption of tacrolimus and therefore treatment with Dailiport may commence orally.

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

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

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

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

Biotransformation
Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4 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 43 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.
When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0.1 to 1.0 mg/kg, QTc prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 ng/mL which is more than 6-fold higher than mean peak concentrations observed with tacrolimus prolonged-release in clinical transplantation.

Embryofoetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic doses and the offspring showed reduced birth weights, viability and growth. A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Ethylcellulose
Hypromellose
Lactose monohydrate
Magnesium stearate

Capsule shell
Brilliant blue FCF (E133)
Allura red AC (E129)
Titanium dioxide (E171)
Sunset yellow FCF (E110)
Gelatin

Printing ink
Shellac Glaze
Allura Red AC Aluminum Lake (E129)
Brilliant Blue FCF Aluminum Lake (E133)
Sunset Yellow FCF Aluminum Lake (E110)
Propylene glycol (E1520)
Lecithin (soya)
Simeticone

6.2 Incompatibilities

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

6.3 Shelf life

2 years

After opening the bag: 1 year

6.4 Special precautions for storage

Store in the original package (aluminium bag) in order to protect from light and moisture.

6.5 Nature and contents of container

PVC/PVDC // aluminium blister with desiccant sealed in aluminium bag.

Packs sizes: 30, 50, 60 (2x30) and 100 (2x50) prolonged-release hard capsules in blister and 30x1, 50x1, 60x1 (2x30) and 100x1 (2x50) prolonged-release hard capsules in unit-dose perforated blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1567

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/10/2019

10 DATE OF REVISION OF THE TEXT

24/03/2025