1. NAME OF THE MEDICINAL PRODUCT

DAGPORT PROLONGED RELEASE HARD CAPSULES 0.5MG
DAGPORT PROLONGED RELEASE HARD CAPSULES 1MG
DAGPORT PROLONGED RELEASE HARD CAPSULES 5MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release hard capsule contains 0.5 mg tacrolimus (as monohydrate).
Each prolonged-release hard capsule contains 1 mg tacrolimus (as monohydrate).
Each prolonged-release hard capsule contains 5 mg tacrolimus (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release hard capsule.

Gelatin capsule size 5 with a light brown body and a light yellow cap, imprinted in black with “0.5 mg”, containing white to yellowish powder or compacted powder (length 10.7 – 11.5 mm).
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).
Gelatin capsule size 0 with a light brown body and a pink cap, imprinted in black with “5 mg”, containing white to yellowish powder or compacted powder (length 21.4 – 22.0 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of transplant rejection in adult kidney or liver allograft recipients and treatment of kidney or liver allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.

4.2 Posology and method of administration

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

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, 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.

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

In *de novo* kidney and liver transplant patients AUC_{0-24} of tacrolimus for 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 Dagport to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, adjustments to the Dagport 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
Dagport 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.
Dagport doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Dagport 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
Dagport 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.
Dagport doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Dagport 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 Dagport
Allograft transplant patients maintained on twice daily tacrolimus immediate-release dosing requiring conversion to once daily Dagport should be converted on a 1:1 (mg:mg) total daily dose basis. Dagport 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 (AUC_{0-24}) for tacrolimus prolonged-release was approximately 10% lower than that for tacrolimus immediate-release. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for tacrolimus prolonged-release is similar to that of tacrolimus immediate-release. When converting from tacrolimus immediate-release to Dagport, 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. Dagport 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 Dagport may need to be reduced.

Treatment of allograft rejection after kidney or liver transplantation

For conversion from other immunosuppressants to once daily Dagport, 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 (C_{24}) 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 Dagport, 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 Dagport, 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 Dagport 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 patients: There is no evidence currently available to indicate that dosing should be adjusted in elderly patients.

Method of administration
Dagport is a once-a-day oral formulation of tacrolimus. It is recommended that the oral daily dose of Dagport be administered once daily in the morning. Dagport 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). Dagport 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 1/5th of the recommended oral dose for the corresponding indication.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypersensitivity to other macrolides.
Allergic to peanut or soya.

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 events, including graft rejection, or other side effects which could be a consequence of either under- or overexposure 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).

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

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

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

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

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

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) should be avoided when taking Dagport 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 drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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

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

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

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

Lymphoproliferative disorders and malignancies
Patients treated with tacrolimus have been reported to develop Epstein-Barr-Virus(EBV)-associated lymphoproliferative disorders (see section 4.8). A combination of immunosuppressives such as antilymphocytic antibodies (e.g. basiliximab, daclizumab) given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Dagport. 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.

Opportunistic infections
Patients treated with immunosuppressants, including Dagport 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 hepatic or renal function or neurological symptoms.

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

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

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

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

Excipients
Dagport capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. The printing ink used to mark Dagport 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 Dagport.

Dagport prolonged release hard capsules 0.5mg
Dagport prolonged release hard capsules 0.5mg contains Sunset yellow FCF (E110), Allura red AC (E129) and tartrazine (E102) which may cause allergic reactions.

Dagport prolonged release hard capsules 1mg
Dagport prolonged release hard capsules 1mg contains Sunset yellow FCF (E110) and Allura red AC (E129) which may cause allergic reactions.

Dagport prolonged release hard capsules 5mg
Dagport prolonged release hard capsules 5mg contains Sunset yellow FCF (E110) and Allura red AC (E129) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.
It is strongly recommended to closely monitor tacrolimus blood levels, as well as QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels
Clinically the following substances have been shown to increase tacrolimus blood levels:
Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole, and voriconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir) and CMV antiviral letermovir. 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,nefazodone and 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.
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:
Strong interactions have been observed with rifampicin, phenytoin, St. John's Wort (*Hypericum perforatum*) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.
Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

<u>Effect of tacrolimus on the metabolism of other medicinal products</u>
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.

<u>Other interactions leading to clinically detrimental effects</u>
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, NSAIDs, ganciclovir or aciclovir).
Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.

As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g. amiloride, triamterene, or spironolactone) should be avoided (see section 4.4).

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

4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Human data show that tacrolimus is able to cross the placenta and infants exposed to tacrolimus *in utero* may be at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress.

The use of tacrolimus during pregnancy has been associated with preterm delivery, neonatal hyperkalemia and renal dysfunction.

Tacrolimus may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly.

Tacrolimus may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure.

Females and males of reproductive potential should consider the use of appropriate contraception prior to starting treatment with tacrolimus.

Due to the need of treatment, tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus.

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

Breast-feeding
Human data demonstrate that tacrolimus is excreted in breast milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving Dagport.

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

Many of the adverse reactions stated below are reversible and/or respond to dose reduction. 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 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
Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders

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

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

Endocrine disorders

rare:	hirsutism

Metabolism and nutrition disorders

very common:	diabetes mellitus, hyperglycaemic conditions, hyperkalaemia
common:	metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia
uncommon:	dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia

Psychiatric disorders

very common:	insomnia
common:	confusion and disorientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare
uncommon:	psychotic disorder

Nervous system disorders

very common:	headache, tremor
common:	nervous system disorders, seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dysaesthesias, writing impaired
uncommon:	encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, speech and language abnormalities, paralysis and paresis, amnesia
rare:	hypertonia
very rare:	myasthenia

Eye disorders

common:	eye disorders, vision blurred, photophobia
uncommon:	cataract
rare:	blindness
not known:	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 cardiac arrest, supraventricular arrthyhmias, cardiomyopathies, ECG investigations abnormal, ventricular hypertrophy, palpitations, heart rate and pulse investigations abnormal
rare:	pericardial effusion
very rare:	echocardiogram abnormal, electrocardiogram QT prolonged, Torsades de Pointes

Vascular disorders

very common:	hypertension
common:	thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders
uncommon:	venous thrombosis deep limb, shock, infarction

Respiratory, thoracic and mediastinal disorders

common:	parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations
uncommon:	respiratory failures, respiratory tract disorders, asthma
rare:	acute respiratory distress syndrome

Gastrointestinal disorders

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

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

common:	rash, pruritus, alopecias, acne, sweating increased
uncommon:	dermatitis, photosensitivity
rare:	toxic epidermal necrolysis (Lyell's syndrome)
very rare:	Stevens Johnson syndrome

Musculoskeletal and connective tissue disorders

common:	arthralgia, back pain, muscle spasms, pain in extremity
uncommon:	joint disorders
rare:	mobility decrease

Renal and urinary disorders

very common:	renal impairment
common:	renal failure, renal failure acute, nephropathy toxic, renal tubular necrosis, urinary

	abnormalities, oliguria, bladder and urethral symptoms
uncommon:	haemolytic uraemic syndrome, anuria
very rare:	nephropathy, cystitis haemorrhagic

Reproductive system and breast disorders

uncommon:	dysmenorrhoea and uterine bleeding

General disorders and administration site conditions

common:	febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed, blood alkaline phosphatase increased, weight increased
uncommon:	weight decreased, influenza like illness, blood lactate dehydrogenase increased, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance
rare:	fall, ulcer, chest tightness, thirst
very rare:	fat tissue increased
not known:	febrile neutropenia

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

4.9 Overdose

Experience with overdose is limited. Several cases of accidental overdose have been reported with tacrolimus; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen, serum creatinine and alanine aminotransferase levels.
No specific antidote to tacrolimus therapy is available. If overdose occurs, general supportive measures and symptomatic treatment should be conducted.
Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus will not be dialysable. In isolated patients with very high plasma levels, haemofiltration or diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Calcineurin inhibitors, ATC code: L04AD02

Mechanism of action
At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.
Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both *in vitro* and *in*

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

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

Lung transplantation
The interim analysis of a recent multicentre study using oral tacrolimus immediate-release discussed 110 patients who underwent 1:1 randomisation to either tacrolimus or ciclosporin. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was

administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus ciclosporin-treated patients (11.5% versus 22.6%) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86% versus 8.57%), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8% in the tacrolimus and 83% in the ciclosporin group.
Another randomised study included 66 patients on tacrolimus versus 67 patients on ciclosporin. Tacrolimus was started as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/ml. The 1-year patient survival was 83% in the tacrolimus and 71% in the ciclosporin group, the 2-year survival rates were 76% and 66%, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the ciclosporin group (1.09 episodes). Obliterative bronchiolitis developed in 21.7% of patients in the tacrolimus group compared with 38.0% of patients in the ciclosporin group ($p = 0.025$). Significantly more ciclosporin-treated patients ($n = 13$) required a switch to tacrolimus than tacrolimus-treated patients to ciclosporin ($n = 2$) ($p = 0.02$) (Keenan et al., Ann Thoracic Surg 1995;60:580).
In an additional two-centre study, 26 patients were randomised to the tacrolimus versus 24 patients to the ciclosporin group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml. The 1-year survival rates were 73.1% in the tacrolimus versus 79.2% in the ciclosporin group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7% versus 45.8%) and at 1 year after lung transplantation (50% versus 33.3%).
The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

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

Intestinal transplantation
Published clinical experience from a single centre on the use of oral tacrolimus immediate-release 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. Dagport 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 Dagport may commence orally. A strong correlation exists between AUC and whole blood trough levels at steady-state for tacrolimus prolonged-release. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

Distribution
In man, the disposition of tacrolimus after intravenous infusion may be described as biphasic. In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is highly bound (> 98.8%) to plasma proteins, mainly to serum albumin and α-1-acid glycoprotein.
Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1300 l (healthy subjects). Corresponding data based on whole blood averaged 47.6 l.

Metabolism
Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4. Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to the pharmacological activity of tacrolimus.

Excretion
Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism, are considered to be responsible for the higher clearance rates observed following transplantation.
The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours.
Following intravenous and oral administration of 14C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

5.3 Preclinical safety data

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

Embryotoxicity was observed in animal studies.

Tacrolimus subcutaneously administered to male rats at a doses of 2 or 3 mg/kg/day (1.6 to 6.4 times the clinical dose range based on body surface area) resulted in a dose-related decrease in sperm count.

Tacrolimus given orally at 1.0 mg/kg (0.8 to 2.2 times the clinical dose range based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction which were indicated by a higher rate of post-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.6 to 6.9 times the clinical dose range based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Ethylcellulose
Hypromellose
Lactose monohydrate
Magnesium stearate

Capsule shell
Dagport prolonged release hard capsules 0.5mg
Brilliant blue FCF
Allura red AC
Titanium dioxide
Sunset yellow FCF
Gelatin
Tartrazine

Dagport prolonged release hard capsules 1mg
Brilliant blue FCF
Allura red AC
Titanium dioxide
Sunset yellow FCF
Gelatin

Dagport prolonged release hard capsules 5mg
Brilliant blue FCF
Allura red AC
Titanium dioxide
Sunset yellow FCF
Gelatin
Erythrosin

Printing ink
Shellac Glaze
Allura Red AC Aluminum Lake
Brilliant Blue FCF Aluminum Lake
Sunset Yellow FCF Aluminum Lake
Propylene glycol
Lecithin
Simeticone

6.2 Incompatibilities

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

6.3 Shelf life

Please refer to outer carton.
After opening the aluminium bag: 3 months (Store at or below 30°C).

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package (aluminium bag) in order to protect from light and moisture.
Keep out of reach of children.

6.5 Nature and contents of container

PVC/PVDC aluminium blister with desiccant sealed in aluminium bag.
Pack size: 50 prolonged-release hard capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. PRODUCT REGISTRANT

Novartis (Singapore) Pte. Ltd.
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Singapore 117439

8. DATE OF REVISION

Jun 2022