PACKAGE INSERT
(For the use of a Registered Medical Practitioner or a Hospital)

1. NAME OF THE MEDICINAL PRODUCT

TACROCIN 0.5, 1, 5 (Tacrolimus Capsules USP 0.5 mg, 1 mg and 5 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TACROCIN 0.5 (Tacrolimus Capsules USP 0.5 mg)
Each Hard Gelatin Capsule Contains:
Tacrolimus USP 0.5 mg

TACROCIN 1 (Tacrolimus Capsules USP 1 mg)
Each Hard Gelatin Capsule Contains:
Tacrolimus USP 1 mg

TACROCIN 5 (Tacrolimus Capsules USP 5 mg)
Each Hard Gelatin Capsule Contains:
Tacrolimus USP 5 mg

3. PHARMACEUTICAL FORM

TACROCIN 0.5 (Tacrolimus Capsules USP 0.5 mg)
Hard Gelatin Capsule
Light yellow/ Light yellow hard gelatin capsules, size "4" imprinted with 'TCR' on cap & 'ABZ 0.5' on body containing white to off white granular powder.

TACROCIN 1 (Tacrolimus Capsules USP 1 mg)
Hard Gelatin Capsule
White / white hard gelatin capsules, size "4" imprinted with 'TCR' on cap & 'ABZ 1' on body containing white to off white granular powder.

TACROCIN 5 (Tacrolimus Capsules USP 5 mg)
Hard Gelatin Capsule
Pink / pink hard gelatin capsules, size "4" imprinted with 'TCR' on cap & 'ABZ 5' on body containing white to off white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Primary immunosuppression in liver and kidney allograft recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive agents.

4.2 Posology and method of administration

Only physicians experienced in immunosuppressive therapy and the management of organ transplant patients should prescribe Tacrolimus. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical

resourced. The physician responsible for maintenance therapy should have complete information requisite for the follow up of the patient.

The dosage recommendations given below are intended to act as a guideline. Tacrolimus doses should be adjusted according to individual patient requirements.

Dosage recommendations

Primary Immunosuppression Dose Levels – Adults

Liver and kidney transplantation: Oral tacrolimus therapy should commence at 0.10 – 0.20 mg/kg/day for liver transplantation and at 0.15 – 0.30 mg/kg/day for kidney transplantation administered as two divided doses. Administration should start approximately 6 hours after the completion of liver transplant surgery and within 24 hours after completion of kidney transplant surgery.

Primary Immunosuppression Dose Levels – Paediatric Patients

Paediatric patients generally require doses 1.5 to 2 times higher than the recommended adult doses to achieve the same blood levels.

Liver and kidney transplantation:

An initial dose of 0.3 mg/kg/day for liver and kidney transplantation should be administered in two divided doses.

Maintenance Therapy Dose Levels

It is necessary to continue immunosuppression with oral Tacrolimus to maintain graft survival. Dose can frequently be reduced during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability of the patient.

If progression of disease occurs (e.g. signs of acute rejection) alteration of the immunosuppressive regimen should be considered. Increase the amount of corticosteroids, introduction of short courses of mono/polyclonal antibodies and increase in the dose of Tacrolimus have been used to manage rejection episodes.

If signs of toxicity (e.g. pronounced adverse event) are noted, the dose of Tacrolimus should be reduced.
When Tacrolimus is administered in combination with a corticosteroid these may often be reduced and in rare cases the treatment has continued as monotherapy.

Therapy Dose Levels for Liver and Kidney Allograft Rejection Resistant to Conventional Immunosuppressive Regimens

In patients experiencing rejections episodes which are unresponsive to conventional immunosuppressive therapy, Tacrolimus treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.

Tacrolimus should be initiated after considering cyclosporin blood concentrations and the clinical condition of the patient. In practice, Tacrolimus therapy has been initiated 12-24 hours after discontinuation of cyclosporin. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin may be affected.

Duration of dosing

For oral dosing the capsules normally have to be taken continuously to suppress graft rejection and no limit for therapy duration can be given.

Mode of Intake

Capsules 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 Pharmacokinetic properties).

Monitoring of Whole Blood Concentrations

Drug level monitoring is recommended during the early post-transplantation period, following dose adjustment of Tacrolimus therapy after switching from another immunosuppressive regimen or following co-administration of drugs which are likely to lead to a drug interaction. Through blood levels of Tacrolimus should also be monitored periodically during maintenance therapy. The frequency of blood level monitoring should be based on clinical needs. As tacrolimus has a long half-life, it can take several days for adjustments in Tacrolimus dosing to be reflected in changes in blood levels.

Patient with Liver Impairment

A dose reduction is necessary.

Patient with Renal Impairment

Careful monitoring of renal function including serial creatinine estimations, calculations of creatinine clearance and monitoring urine output is recommended.

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

4.3 Contraindications

Tacrolimus is contra-indicated in patients hypersensitive to tacrolimus or other macrolides, or to other ingredients of the capsules.

4.4 Special warnings and precautions for use

Post-Transplant Diabetes Mellitus (PTDM)

Post transplant insulin dependent diabetes mellitus (PTDM - use of insulin for 30 or more consecutive days, with < 5 day gap, by patients without a prior history of insulin or non insulin-dependent diabetes mellitus) was reported in 20% (30/151) and 6% (17/281) of

tacrolimus treated kidney transplant patients in the U.S. and European randomised trials respectively. The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these patients at one year and in 50% at two years post transplant. Black and Hispanic patients were found to be at increased risk of development of PTDM in the U.S. trial. The risk benefit ratio should be carefully considered before using tacrolimus in kidney transplant patients with a pre-transplant diabetic condition.

In liver transplantation PTDM was reported in 18% (42/239) and 11% (26/239) of tacrolimus treated patients and was reversible in 45% and 31% of these patients at one year post transplant in the U.S. and European randomised trials respectively**.**

Insulin-dependent post-transplant diabetes mellitus was reported in 13% (10/75) and 22% (29/132) of tacrolimus treated heart transplant patients receiving mycophenolate mofetil or azathioprine and was reversible in 30% and 17% of these patients at one year post transplant, in the US and European randomised studies, respectively.

Neurotoxicity
Neurological and CNS disorders have been reported with tacrolimus therapy. Symptoms include tremor, headache, changes in motor function, sensory function or mental status, insomnia, seizures, coma and delirium. Patients experiencing such events should be carefully monitored. In cases of severe or worsening neurological disorder, adjustment of the immunosuppressive regimen should be considered.

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 (PRCA)
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 cause renal impairment charactered by increases in serum creatinine as a result of a reduced glomerular filtration rate, particularly when used in high doses. These changes have been observed to be dose dependent and improvement have been associated with reduced dosing. The mechanism leading to these changes is not fully understood. Use of tacrolimus with sirolimus in heart transplantation patients in a US study was associated with increased risk of renal function impairment, and is not recommended. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced.

Care should be taken in using tacrolimus with other nephrotoxic drugs. In particular, tacrolimus should not be used simultaneously with cyclosporin. Tacrolimus or cyclosporin should be discontinued at least 24 hours prior to initiating the other. In the presence of

elevated tacrolimus or cyclosporin concentrations, dosing with the other drug usually should be further delayed.

Hyperkalaemia
Mild to severe hyperkalaemia was reported in patients treated with tacrolimus, especially in patients with renal impairment. Patients may require treatment, and should avoid high dietary potassium intake. Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during tacrolimus therapy.

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

Herbal preparations containing St. John's wort (Hypericum perforatum) or other herbal preparations should be avoided when taking tacrolimus due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus (see section Interactions with other medicinal products and other forms of interaction).

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 Posology and method of administration and Interaction with other medicinal products and other forms of interaction).

High potassium intake or potassium-sparing diuretics should be avoided (see section Interaction with other medicinal products and other forms of interaction).

Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see Interaction with other medicinal products and other forms of interaction.

Vaccination
Immunosuppressant 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.

Malignancies

As with other potent immunosuppressive compounds, patients treated with tacrolimus are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. In patients switched to tacrolimus, this may be attributable to over-immunosuppression before commencing therapy with this agent. Very young (<2 years), EBV-sero-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV serology should be ascertained before starting treatment with tacrolimus. During treatment, careful monitoring is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma.

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposures to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section Undesirable effects).

Infections
Like other immunosuppressants, tacrolimus predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections. Oversuppression of the immune system can also increase susceptibility to opportunistic infections, sepsis and fatal infections. 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.

Hypertension
Hypertension is a common adverse effect of tacrolimus therapy. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating tacrolimus-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction.

Myocardial Hypertrophy
Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies have been observed in a few cases in association with administration of tacrolimus. Most of these have been reversible, occurring primarily in patients having tacrolimus blood trough levels higher than the recommended level. Mean tacrolimus whole blood trough concentrations during the period prior to diagnosis of myocardial hypertrophy in 20 patients with pre and post treatment echo cardiograms ranged from 10.6 to 53.3 ng/mL in infants (N= 10, age 0.4 to 2 years), 4.0 to 45.7 ng/mL in children (N= 7, age 2 to 15 years) and 10.9 to 24.3 ng/mL in adults (N= 3, age 37 to 45 years). Other factors observed to increase the risk of these clinical conditions are, for example, previously existing heart diseases, corticosteroid usage, hypertension, renal or hepatic dysfunction, and fluid overload. Accordingly, high-risk

patients should be monitored, e.g., with echocardiography or ECG. If abnormalities develop, dose reduction of tacrolimus therapy, or change of treatment to other 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 Interaction with other medicinal products and other forms of interaction).

Conversion between agents

Conversion between tacrolimus formulations
Various formulations of tacrolimus are available. Medication errors have resulted in incorrect dosing or unsupervised switching between tacrolimus formulations. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under exposure or over exposure to tacrolimus. Therefore it is appropriate to prescribe and dispense tacrolimus by tradename, taking care to specify appropriate daily dosing (e.g. twice daily for capsules or once daily for prolonged-release capsules). It should be emphasised that patients, once titrated to an effective dose of a particular formulation of tacrolimus, should not be changed to another formulation of tacrolimus without blood trough level monitoring, clinical assessment and re-titration (see **Posology and method of administration**).

Conversion with cyclosporin
Tacrolimus should not be administered concurrently with cyclosporin as the half-life of the latter may be increased. Synergistic/additive nephrotoxic effects can also occur. Care should be taken when administering tacrolimus to patients who have previously received cyclosporin and when converting patients from cyclosporin- to tacrolimus -based therapy. It is recommended that cyclosporin blood levels are monitored prior to the administration of tacrolimus. The most appropriate time to initiate tacrolimus therapy should be based upon information on cyclosporin blood levels and the clinical condition of the patient. Dosing may be delayed in the presence of elevated cyclosporin levels. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin may be affected. A 24 hour interval between stopping cyclosporin and starting tacrolimus has been commonly used.

Patients switched to tacrolimus rescue therapy should not be given anti-lymphocyte treatment concomitantly.

Excipients

As Tacrolimus capsule contains lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

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 drugs or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is therefore recommended to monitor tacrolimus blood levels whenever drugs which have the potential to alter CYP3A metabolism are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Inhibitors of Metabolism

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), CMV antiviral letermovir and amiodarone. Concomitant use of these drugs may require decreased tacrolimus doses in nearly all patients.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.

The herbal remedy schisandra sphenanthra extract inhibits CYP3A4 and may increase the blood levels of tacrolimus.

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 tarcrolimus and should therefore be avoided.

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

Inducers of Metabolism

Clinically the following substances have been shown to decrease tacrolimus blood levels:
Strong interactions have been observed with rifampicin, phenytoin or St John's Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.
High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.

Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

Effect of Tacrolimus on the Metabolism of Other Drugs

Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with drugs known to be metabolised by CYP3A4 may affect the metabolism of such drugs.

The half-life of cyclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporin.

Tacrolimus have 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. Available data suggests that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.

Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

Other potential interactions that may increase systemic exposure of tacrolimus: Prokinetic agents such as metoclopramide and cisapride, Cimetidine, Magnesium-aluminum-hydroxide.

Other Interactions which have led to Clinically Detrimental Effects
Concurrent use of tacrolimus with drugs 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.

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.

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

4.6 Pregnancy, lactation and fertility

Use in 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 of 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.

Use in Lactation
Tacrolimus is excreted into breast milk. It is therefore recommended that mothers should not breast-feed while receiving tacrolimus.

Effects on fertility
A negative effect of Tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats (see section preclinical safety data).

4.7 Effects on ability to drive and use machines

Tacrolimus may cause visual and neurological disturbances. Patients treated with tacrolimus who are affected by such disorders should not drive a car or operate dangerous machinery.

4.8 Undesirable effects

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

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 drug reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse drug reactions compared with intravenous use. Adverse drug reactions are listed below in descending order by frequency of occurrence: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000, including isolated reports), not known (cannot be estimated from the available data).

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, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal
uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia, thrombotic microangiopathy
not known : agranulocytosis, haemolytic anaemia, pure red cell aplasia (observed during post-marketing)

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see **PRECAUTIONS**).

Endocrine disorders

rare: hirsutism

Metabolism and nutrition disorders

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

Psychiatric disorders

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

Nervous system disorders

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

rare: hypertonia
very rare: myasthenia

Eye disorders

common: vision blurred, photophobia, eye disorders
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: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal, QT prolongation, Torsades de pointes.
rare: pericardial effusion
very rare: echocardiogram abnormal

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal disorders

very common: diarrhoea, nausea
common: gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms

uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastrooesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

Hepatobiliary disorders

very common: liver function test abnormal
common: bile duct disorders, cholestasis and jaundice, hepatocellular damage and hepatitis
rare: hepatitic artery thrombosis, venoocclusive liver disease
very rare: hepatic failure

Skin and subcutaneous disorders

common: pruritus, rash, 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, muscle cramps, pain in limb, back pain
uncommon: joint disorders
rare: mobility decrease

Renal and urinary disorders

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

Reproductive system and breast disorders

uncommon: dysmenorrhoea and uterine bleeding

General disorders and administration site conditions

common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed
uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased
rare: thirst, fall, chest tightness, mobility decreased, ulcer
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 supratherapeutic 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 overdosage is limited. Several cases of accidental overdosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen and elevated serum creatinine concentrations and increase in alanine aminotransferase levels.

No specific antidote to tacrolimus therapy is available. If overdosage 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 and diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of absorbents (such as activated charcoal) may be helpful, if used shortly after intake.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tacrolimus is a macrolide lactone with potent *in vitro* and *in vivo* immunosuppressive activity. Studies suggest that tacrolimus inhibits the formation of cytotoxic lymphocytes which are regarded as being primarily 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 and -3 and gamma-interferon and the expression of the interleukin-2 receptor. At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP), which is responsible for the intracellular accumulation of the compound. A complex of tacrolimus-FKBP-12, calcium, calmodulin and calcineurin is formed and the phosphatase activity of calcineurin inhibited.

Studies in animals and man have shown that tacrolimus is able to prevent and treat graft rejection following transplantation of the liver, kidney, and other solid organs.

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.

Following oral administration of tacrolimus capsules peak concentrations (C_{max}) of tacrolimus in blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20% - 25%.

After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients.
The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.
In a study of stable renal transplant patients who were administered tacrolimus capsules immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption of tacrolimus and therefore commencement of tacrolimus therapy with an oral dose or early conversion of liver transplant patients from intravenous to oral therapy is possible.

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

Distribution and elimination
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.

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver and kidney transplant patients, values of 4.1 l/h and 6.7 l/h respectively, have been observed. Paediatric liver transplant recipients have a TBC approximately twice that of adult liver transplant patients. 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.
There is evidence that pharmacokinetics of tacrolimus change with improving clinical conditions of the patients. In liver transplant patients, the mean oral dose was decreased by 28% from day 7 to month 6 after transplantation to maintain similar mean trough levels of tacrolimus. Change in clearance and/or bioavailability were suggested as probable causes for this effect.

The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours. In adult and paediatric liver transplant patients, it averaged 11.7 hours and 12.4 hours, respectively, compared with 15.6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

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

Excretion
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.

Clinical Studies in Patients with Lupus Nephritis

Patients with lupus nephritis who were refractory to steroid monotherapy and exhibited clinical signs of chronic nephritis with immunological activity were treated with tacrolimus capsules (a dose of 3mg, once daily after supper) for 28 weeks in the Phase III trial. The rate of change in the total score* of disease activity at the final measurement was –32.9%. The rate of change in the actual values of daily urinary protein excretion and complement (C3), which are indices of chronic nephritis and immunological activity, respectively, were –60.8% and 16.4%, and the change in creatinine clearance (CCr) was –22.0%.

	Tacrolimus group [n=27]	Placebo group [n=34]	95% confidence intervals for the differences between groups
The rate of change in the total score of disease activity* (%), mean ± S.D.	–32.9 ± 31.0	2.3 ± 38.2	–
The rate of change in the actual value of daily urinary protein excretion (%), median (1st quartile, 3rd quartile)	–60.8 (–73.7, –37.2)	8.7 (–14.0, 90.0)	[–115.0 to –48.7]
The rate of change in the actual value of complement (C3) (%), median (1st quartile, 3rd quartile)	16.4 (10.3, 27.5)	–2.8 (–11.1, 18.2)	[8.5 to 26.7]

The rate of change in the actual value of CCr (%), median (1st quartile, 3rd quartile)	–22.0** (–33.5, –4.2)	–1.4 (–19.3, 16.9)	[–30.5 to –3.4]

*Total score of disease activity consists of the sum of the scores (a 4-point scale, ranging from 0 to 3 per item) of 5 items: daily urinary protein excretion, urinary red blood cells, serum creatinine, anti-ds DNA antibody, and complement (C3).
** As for the evaluation of CCr only, the number of cases for the tacrolimus group was 26.

The major adverse reactions or abnormalities in clinical laboratory findings due to tacrolimus capsules in 65 patients with lupus nephritis in Phase II and Phase III trials were β2 microglobulin urine increased (27.3%, 12/44), urinary NAG increased (22.2%, 14/63), nasopharyngitis (15.4%, 10/65), hyperuricaemia (14.1%, 9/64), leukocytosis (14.1%, 9/64), creatinine increased (12.5%, 8/64), diarrhoea (12.3%, 8/65), blood pressure increased (10.8%, 7/65), and hyperglycaemia (10.9%, 7/64).

Preclinical Safety Data

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

Each hard gelatin capsule contains:
Hypromellose
Croscarmellose Sodium
Lactose anhydrous
Magnesium Stearate

TACROCIN 0.5 (Tacrolimus Capsules USP 0.5 mg)
Light yellow / light yellow hard gelatin capsules, size “4” imprinted with “TCR” on cap & “ABZ 0.5” on body
Capsule shell contains gelatin, Iron oxide yellow, and Titanium dioxide

TACROCIN 1 (Tacrolimus Capsules USP 1 mg)
White / White hard gelatin capsules, size “4” imprinted with “TCR” on cap & “ABZ 1” on body
Capsule shell contains gelatin and Titanium dioxide

TACROCIN 5 (Tacrolimus Capsules USP 5 mg)

Pink / pink hard gelatin capsules, size “4” imprinted with ‘TCR’ on cap & ‘ABZ 5’ on body
Capsule shell contains gelatin, Iron oxide red, and Titanium dioxide

6.2 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture and light.

6.3 Nature and contents of container

TACROCIN capsules are available in aluminium / aluminium blister pack of 10 capsules, each carton contains 5 such blisters.

7. NAME AND ADDRESS OF PRODUCT REGISTRANT

Accord Healthcare Private Limited
6 Shenton Way, OUE Downtown #38-01
Singapore, 068809

8. DATE OF REVISION OF PACKAGE INSERT

March 2021