For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

TACROTOR

1. **Generic Name**

   Tacrolimus Capsules I.P.

2. Qualitative and quantitative composition

TACROTOR 0.5

Each hard gelatin capsule contains:

Tacrolimus I.P……..0.5 mg

Approved colours used in capsule shell.

The excipients used are Lactose, Croscarmellose Sodium, Hydroxypropyl Methyl Cellulose, Propanol – E, Magnesium Stearate, HEG Capsule Size 4.

TACROTOR 1

Each hard gelatin capsule contains:

Tacrolimus I.P……..1 mg

Approved colours used in capsule shell.

The excipients used are Lactose, Croscarmellose Sodium, Hydroxypropyl Methyl Cellulose, Propanol – E, Magnesium Stearate, HEG Capsule Size 4.

3. Dosage form and strength

Dosage form: Hard Gelatin Capsules

Strength: 0.5 mg & 1 mg.

4. Clinical particulars

4.1 Therapeutic indication

TACROTOR is indicated for prophylaxis of organ rejection in patients receiving allogenic kidney transplant

4.2 Posology and method of administration

Posology

The daily recommended dose is as directed by the Physician.

Method of administration

TACROTOR hard gelatin capsules should be administered orally.

4.3 Contraindications

- Hypersensitivity to tacrolimus, or to any of the excipients
- Hypersensitivity to other macrolides

4.4 Special warnings and precautions for use

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has

led to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist.

TACROTOR 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 prolonged-release formulation TACROTOR.

For prophylaxis of transplant rejection in adult heart allograft recipients' clinical data are not yet available for TACROTOR.

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 - 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 monitoredto 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 TACROTOR due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity.

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.

High potassium intake or potassium-sparing diuretics should be avoided.

Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects.

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

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 Prograf treated patients on rare occasions and may also occur with TACROTOR. 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 TACROTOR, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval and may cause *Torsades de Pointes*. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure.

Lymphoproliferative disorders and malignancies

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

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections including opportunistic infections

Patients treated with immunosuppressants, including TACROTOR are at increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal) such as BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). Patients are also at an increased risk of infections with viral hepatitis (for example, hepatitis B and C reactivation and de novo infection, as well as hepatitis E, which may become chronic).

These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis

in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms. Prevention and management should be in accordance with appropriate clinical guidance.

Posterior reversible encephalopathy syndrome (PRES)

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

Eye disorders

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

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.

Excipients

TACROTOR 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 TACROTOR 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 TACROTOR.

4.5 Drugs interactions

Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances 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.

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, voriconazole and isavuconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir, and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir), or the CMV antiviral letermovir, the pharmacokinetic enhancer cobicistat, and the tyrosine kinase inhibitors nilotinib and imatinib. Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, nefazodone and (Chinese) herbal remedies containing extracts of Schisandra sphenanthera.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethindrone, quinidine, tamoxifen, (triacetyl)oleandomycin.

Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.

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

<u>Other interactions potentially leading to increased tacrolimus blood levels</u>

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.

<u>CYP3A4 inducers potentially leading to decreased tacrolimus blood levels</u>

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.

Tacrolimus has been shown to increase the blood level of phenytoin.

As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.

Limited knowledge of interactions between tacrolimus and statins is available. Clinical data suggest that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.

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

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

Other interactions leading to clinically detrimental effects

Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, 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.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Human data reported show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse reactions on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In case of in utero

exposure, monitoring of the newborn for the potential adverse events of tacrolimus is recommended (in particular effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn (incidence 8 of 111 neonates, i.e. 7.2 %) which, however normalises spontaneously.

In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity.

Breast-feeding

Human data reported demonstrate that tacrolimus is excreted in breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving TACROTOR.

Fertility

A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.

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 (TACROTOR) on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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

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

The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Cases of 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 TACROTOR.

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.

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 arrhythmias, cardiomyopathies, ventricular hypertrophy, palpitations

rare: pericardial effusion

very rare: 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, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying

rare: pancreatic pseudocyst, subileus

Hepatobiliary disorders

common: bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice

rare: venoocclusive 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 decreased

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

uncommon: influenza like illness, 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

Investigations

very common: liver function tests abnormal

common: blood alkaline phosphatase increased, weight increased

uncommon: amylase increased, ECG investigations abnormal, heart rate and pulse investigations

abnormal, weight decreased, blood lactate dehydrogenase increased

very rare: echocardiogram abnormal, electrocardiogram QT prolonged

Injury, poisoning and procedural complications

common: primary graft dysfunction

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

Description of selected adverse reactions

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

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine

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 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.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, calcineurin inhibitors,

ATC code: L04AD02

Results from reported clinical trials performed with once-daily tacrolimus TACROTOR

Liver transplantation

The efficacy and safety of TACROTOR and Prograf, both in combination with corticosteroids reported studies, 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 TACROTOR group (N=237) and 29.3% in the Prograf group (N=234). The treatment difference (TACROTOR ‑ Prograf) was 3.3% (95% confidence interval [-5.7%, 12.3%]).The 12-month patient survival rates were 89.2% for TACROTOR and 90.8% for Prograf; in the TACROTOR arm 25 patients died (14 female, 11 male) and in the Prograf arm 24 patients died (5 female, 19 male). 12-month graft survival was 85.3% for TACROTOR and 85.6% for Prograf.

Kidney transplantation

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

The efficacy and safety of Prograf, ciclosporin and TACROTOR, all in combination with basiliximab antibody induction, MMF and corticosteroids, was compared in 638 *de novo* kidney transplant recipients in a reported study. 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 TACROTOR group (N=214), 15.1% in the Prograf group (N=212) and 17.0% in the ciclosporin group (N=212). The treatment difference was -3.0% (TACROTOR-ciclosporin) (95.2% confidence interval [-9.9%, 4.0%]) for TACROTOR vs. ciclosporin and -1.9% (Prograf-ciclosporin) (95.2% confidence interval [-8.9%, 5.2%]) for Prograf vs. ciclosporin. The 12-month patient survival rates were 98.6% for TACROTOR, 95.7% for Prograf and 97.6% for ciclosporin; in the TACROTOR arm 3 patients died (all male), in the Prograf 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 TACROTOR, 92.9% for Prograf and 95.7% for ciclosporin.

Clinical efficacy and safety of Prograf capsules bid in primary organ transplantation

In prospective reported studies oral Prograf 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 Prograf in these published studies appeared to be similar to what was reported in the large studies, where Prograf 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 reported multicentre study using oral Prograf 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 reported 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 reported 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.

In a reported study, 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 reported 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 reported study using oral Prograf 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 reported clinical experience from a single centre on the use of oral Prograf 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.

5.3 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. TACROTOR is a prolonged-release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to maximum blood concentration (C_{max}) of approximately 2 hours (t_{max}).

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

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

A strong correlation exists between AUC and whole blood trough levels at steady-state for TACROTOR. 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 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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

When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0.1 to 1.0 mg/kg, QTc prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 ng/mL which is more than 6-fold higher than mean peak concentrations observed with TACROTOR in reported study clinical transplantation.

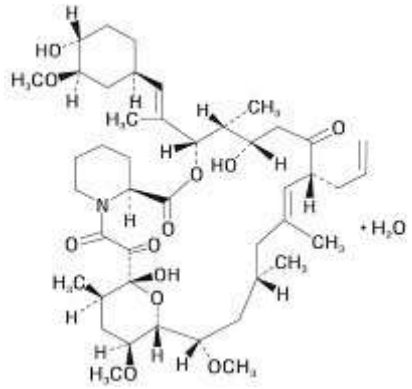
Embryofoetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals of reported study. In rats, female reproductive function including birth was impaired at toxic doses and the offspring showed reduced birth weights, viability and growth.

In a reported studies, a negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.

7. Description

Tacrolimus is a macrolide immunosuppressant produced by Streptomyces tsukubaensis. Chemically, tacrolimus is designated as

[3S [3R* [E (1S*, 3S* 4S*)], 4S*, 5R*, 8S*, 9E, 12R* 14R* 15S* 16R* 18S* 19S* 26aR*]] -5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate. The chemical structure of tacrolimus is:



Tacrolimus has a molecular formula of $C_{44}H_{69}NO_{12}•H_2O$ and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder.

TACROTOR 0.5

Tacrolimus Capsules are Grey (Cap)/ White (Body) hard gelatin capsules filled with white colour powder. The excipients used are Lactose, Croscarmellose Sodium, Hydroxypropyl Methyl Cellulose, Propanol – E, Magnesium Stearate, HEG Capsule Size 4.

TACROTOR 1

Tacrolimus Capsules are Red (Cap)/ White (Body) hard gelatin capsules filled with white colour powder. The excipients used are Lactose, Croscarmellose Sodium, Hydroxypropyl Methyl Cellulose, Propanol – E, Magnesium Stearate, HEG Capsule Size 4.

8. Pharmaceutical particulars

8.1 Incompatibilities

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

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

TACROTOR is available in strips of 10 capsules.

8.4 Storage and handing instructions

Store protected from light and moisture at a temperature not exceeding 30°C.

Keep all medicines out of reach of children.

9. Patient counselling information

TACROTOR

(Tacrolimus Capsules I.P)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What TACROTOR is and what it is used for

9.2.What you need to know before you take TACROTOR

9.3.How to take TACROTOR

9.4.Possible side effects

9.5.How to store TACROTOR

9.6.Contents of the pack and other information

9.1 What TACROTOR is and what it is used for

TACROTOR contains the active substance tacrolimus. It is an immunosuppressant.

TACROTOR is indicated for prophylaxis of organ rejection in patients receiving allogenic kidney transplant. TACROTOR is used in adults.

9.2 What you need to know before you take TACROTOR

Do not take TACROTOR

- if you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of TACROTOR.
- if you are allergic to sirolimus or to any macrolide-antibiotic (e.g. erythromycin, clarithromycin, josamycin).

Warnings and precautions

Prograf and TACROTOR both contain the active substance, tacrolimus. However, TACROTOR is taken once daily, whereas Prograf is taken twice daily. This is because TACROTOR capsules allow for a prolonged release (more slow release over a longer period) of tacrolimus. TACROTOR and Prograf are not interchangeable.

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

- if you are taking any medicines mentioned below under 'Other medicines and TACROTOR'.
- if you have or have had liver problems
- if you have diarrhoea for more than one day
- if you feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting

- if you have an alteration of the electrical activity of your heart called "QT prolongation".

Tell your doctor immediately if during treatment you suffer from:

Problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.

Your doctor may need to adjust your dose of TACROTOR.

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

You should limit your exposure to the sun and UV (ultraviolet) light whilst taking TACROTOR. This is because immunosuppressants could increase the risk of skin cancer. Wear appropriate protective clothing and use a sunscreen with a high sun protection factor.

Children and adolescents

The use of TACROTOR is not recommended in children and adolescents under 18 years.

Other medicines and TACROTOR

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

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

TACROTOR blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking TACROTOR, which may require interruption, an increase or a decrease in TACROTOR dose. In particular, you should tell your doctor if you are taking or have recently taken medicines like:

- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g. ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, and isavuconazole, erythromycin, clarithromycin, josamycin, and rifampicin
- letermovir, used to prevent illness caused by CMV (human cytomegalovirus)
- HIV protease inhibitors (e.g ritonavir, nelfinavir, saquinavir), the booster medicine cobicistat, and combination tablets, used to treat HIV infection
- HCV protease inhibitors (e.g. telaprevir, boceprevir, and the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir), used to treat hepatitis C infection
- nilotinib and imatinib (used to treat certain cancers)
- mycophenolic acid, used to suppress the immune system to prevent transplant rejection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)

- cisapride or the antacid magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill or other hormone treatments with ethinylestradiol, hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g. nifedipine, nicardipine, diltiazem and verapamil)
- anti-arrhythmic drugs (amiodarone) used to control arrhythmia (uneven beating of the heart)
- medicines known as "statins" used to treat elevated cholesterol and triglycerides
- phenytoin or phenobarbital, used to treat epilepsy
- the corticosteroids prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression
- Herbal preparations containing St. John's Wort (Hypericum perforatum) or extracts of Schisandra sphenanthera.

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

Your doctor also needs to know if you are taking potassium supplements or certain diuretics used for heart failure, hypertension and kidney disease, (e.g. amiloride, triamterene, or spironolactone), non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes, while you take TACROTOR.

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

TACROTOR with food and drink

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

Pregnancy and breast-feeding

If you are, think you might be or are planning to become pregnant, ask your doctor for advice before using TACROTOR.

TACROTOR passes into breast milk. Therefore, you should not breast-feed whilst using TACROTOR.

Driving and using machines

Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking TACROTOR. These effects are more frequent if you also drink alcohol.

TACROTOR contains lactose, sodium and lecithin (soya)

TACROTOR contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

The printing ink used on TACROTOR capsules contains soya lecithin. If you are allergic to peanut or soya, talk to your doctor to determine whether you should use this medicine.

9.3 How to take TACROTOR

Always take TACROTOR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. This medicine should only be prescribed to you by a doctor with experience in the treatment of transplant patients.

Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine. This medicine should be taken once a day. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial daily doses just after transplantation will generally be in the range of 0.10 – 0.30 mg per kg body weight per day depending on the transplanted organ. When treating rejection, these same doses may be used.

Your dose depends on your general condition and on which other immunosuppressive medication you are taking.

Following the initiation of your treatment with TACROTOR, frequent blood tests will be taken by your doctor to define the correct dose. Afterwards regular blood tests by your doctor will be required to define the correct dose and to adjust the dose from time to time. Your doctor will usually reduce your TACROTOR dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take.

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

TACROTOR is taken orally once daily in the morning. Take TACROTOR on an empty stomach or 2 to 3 hours after a meal. Wait at least 1 hour until the next meal. Take the capsules immediately following removal from the blister. The capsules should be swallowed **whole** with a glass of water. Do not swallow the desiccant contained in the foil wrapper.

If you take more TACROTOR than you should

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

If you forget to take TACROTOR

If you have forgotten to take your TACROTOR capsules in the morning, take them as soon as possible on the same day. Do not take a double dose the next morning.

If you stop taking TACROTOR

Stopping your treatment with TACROTOR may increase the risk of rejection of your

transplanted organ. Do not stop your treatment unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, TACROTOR can cause side effects, although not everybody gets them.

TACROTOR reduces your body's defence mechanism (immune system), which will not be as good at fighting infections. Therefore, you may be more prone to infections while you are taking TACROTOR.

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

Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), agranulocytosis (a severely lowered number of white blood cells), haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown) and febrile neutropenia (a decrease in the type of white blood cells which fight infection, accompanied by fever) have been reported. It is not known exactly how often these side effects occur.

Very common side effects (may affect more than 1 in 10 people):

- Increased blood sugar, diabetes mellitus, increased potassium in the blood
- Difficulty in sleeping
- Trembling, headache
- Increased blood pressure
- Liver function tests abnormal
- Diarrhoea, nausea
- Kidney problems

Common side effects (may affect up to 1 in 10 people):

- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts
- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood saltsee
- Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- Fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- Blurred vision, increased sensitivity to light, eye disorders
- Ringing sound in your ears

- Reduced blood flow in the heart vessels, faster heartbeat
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- Shortness in breath, disorders of the respiratory tissues in the lung, collection of liquid around the lung, inflammation of the pharynx, cough, flu-like symptoms
- Stomach problems such as inflammation or ulcer causing abdominal pain or diarrhoea, bleeding in the stomach, inflammation or ulcer in the mouth, collection of fluid in the belly, vomiting, abdominal pain, indigestion, constipation, passing wind, bloating, loose stools
- Bile duct disorders, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- Itching, rash, hair loss, acne, increased sweating
- Pain in joints, limbs, back and feet, muscle spasms
- Insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- General weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling of temperature disturbed
- Insufficient function of your transplanted organ

Uncommon side effects (may affect up to 1 in 100 people):

- Changes in blood clotting, reduction in the number of all types of blood cells
- Dehydration, inability to urinate
- Abnormal blood test results: reduced protein or sugar, increased phosphate, increase of the enzyme lactate dehydrogenase
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- Clouding of the eye lens, impaired hearing
- Irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
- Blood clot in a vein of a limb, shock
- Difficulties in breathing, respiratory tract disorders, asthma
- Obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
- Inflammation of the skin, burning sensation in the sunlight

- Joint disorders
- Painful menstruation and abnormal menstrual bleeding
- Multiple organ failure, flu-like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, weight loss

Rare side effects (may affect up to 1 in 1,000 people):

- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Blindness, deafness
- Collection of fluid around the heart
- Acute breathlessness
- Cyst formation in your pancreas
- Problems with blood flow in the liver
- Serious illness with blistering of skin, mouth, eyes and genitals; increased hairiness
- Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer

Very rare side effects (may affect up to 1 in 10,000 people):

- Muscular weakness
- Abnormal heart scan
- Liver failure
- Painful urination with blood in the urine
- Increase of fat tissue

Not known (frequency cannot be estimated from the available data):

- Abnormality of the optic nerve (optic neuropathy)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store TACROTOR

Store protected from light and moisture at a temperature not exceeding 30°C.

9.6 Contents of the pack and other information

What TACROTOR contains

The active substances TACROTOR contains Tacrolimus.

TACROTOR 0.5

Tacrolimus……0.5 mg

TACROTOR 1

Tacrolimus…..1 mg

The excipients used are Lactose, Croscarmellose Sodium, Hydroxypropyl Methyl Cellulose, Propanol-E, Magnesium Stearate, HEG Capsule Size 4.

10. Details of manufacturer

Manufactured by:

The Madras Pharmaceuticals

137-B, Old Mahabalipuram Road, Karapakkam, Chennai-600096.

11. Details of permission or licence number with date

Mfg Lic No. 247 issued on 30.05.2013

12. Date of revision

Jun/2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ TACROTOR 0.5, 1 mg/JUN-20/02/PI