FRONT

VITAC02-var (MY SIN)

Tacrocord™ Capsules

DESCRIPTION

Tacrocord 0.5 Capsules 0.5 mg:
Opaque light yellow color, size "4" hard gelatin capsules imprinted with "C5" "0.5mg" on cap with black ink, containing white to off white granular powder.

Tacrocord 1 Capsules 1 mg:
Opaque white color, size "4" hard gelatin capsules imprinted with "C6" "1mg" on cap with black ink, containing white to off white granular powder.

Tacrocord 5 Capsules 5 mg:
Opaque grayish red color, size "4" hard gelatin capsules imprinted with "C7" "5mg" on cap with black ink, containing white to off white granular powder.

COMPOSITION

Tacrocord 0.5 Capsules 0.5 mg:
Each hard gelatin capsule contains: Tacrolimus 0.5mg

Tacrocord 1 Capsules 1 mg:
Each hard gelatin capsule contains: Tacrolimus 1mg

Tacrocord 5 Capsules 5 mg:
Each hard gelatin capsule contains: Tacrolimus 5mg

PHARMACODYNAMICS

Pharmacotherapeutic group: Calcineurin inhibitors, ATC code: L04AD02

Mechanism of Action and Pharmacodynamic Effects
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 lymphokine genes.

Tacrolimus is a highly immunosuppressive agent and has proven activity in both in vivo and in vitro 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.

PHARMACOKINETICS

Absorption
Tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus capsules, peak concentrations (Cmax) of tacrolimus in blood are achieved in approximately 1-3 hours. In some patients, tacrolimus may appear 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%.

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.

Bile flow does not influence the absorption of tacrolimus.

A strong correlation exists between AUC and whole blood trough levels at steady-state. 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 1300L. Corresponding data based on whole blood data averaged 47.6L.

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25L/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. Paediatric liver transplant recipients may have a total body clearance 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 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. 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
Tacrolimus is almost completely metabolised prior to elimination, bile being the principal route of elimination.

INDICATIONS

Primary immunosuppression in liver and kidney allograft recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive agents. It is recommended that Tacrocord be used concomitantly with adrenal corticosteroids.

Only for Tacrolimus Capsules 0.5mg and 1mg
Lupus nephritis (in a case where the effect of steroids is insufficient or administration of steroids is difficult because of their adverse reactions). For lupus nephritis, the efficacy and safety of this product for patients in an acute phase with high disease activity has not been established.

CONTRAINDICATIONS

Tacrocord should not be given to:
- Hypersensitivity to tacrolimus or other macrolides
- Hypersensitivity to any of the excipients of Tacrocord

WARNINGS AND PRECAUTIONS

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under or 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.

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 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.

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.

Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes.

Vaccination
IImmunosuppressants 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, has been observed on rare occasions. Most cases have been reversible, occurring primarily in children 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, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of tacrolimus therapy, 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. Patients switched to tacrolimus therapy should not receive anti-lymphocyte treatment concomitantly. Very young (< 2 years), EBV-VCA-negative children 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 tacrolimus. 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 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. As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown.

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 control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Infections including opportunistic infections
Patient treated with immunosuppressants, including tacrolimus are at increased risk of 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 patients with deteriorating hepatic or renal function or neurological symptoms. Prevention and management should be in accordance with appropriate clinical guidance.

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.

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

Warnings and precautions for patients with Lupus nephritis
The safety of this product in children has not been established in lupus nephritis (no clinical experiences).

Patients with lupus nephritis also need special attention because the renal disorder may become aggravated as the lupus nephritis progresses.

Since patients with lupus nephritis are more likely to suffer from hyperlipidaemia, hypertension, or the like which is considered to be a risk factor for the development of the coronary artery disease associated with systemic lupus erythematosus, the underlying disease, patients being treated with this product should also receive appropriate therapy for these risk factors of the coronary diseases.

In patients with lupus nephritis, creatinine clearance was shown to decrease after 28 weeks of treatment. There are only a few results from clinical trials in patients with lupus nephritis lasting longer than 28 weeks, and therefore the long-term safety of this product has not been established.

PREGNANCY AND LACTATION

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

The use of tacrolimus during pregnancy has been associated with preterm delivery, neonatal hyperkalemia and renal dysfunction. Tacrolimus may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly. Tacrolimus may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure.

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

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

Lactation
Tacrolimus is excreted into human breast milk. The effects of tacrolimus on the breastfed infant, or on milk production are unknown. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving tacrolimus.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

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

DRUG INTERACTIONS

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 medicinal products 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 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 are used concomitantly and to interrupt or 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) or 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.

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*.

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.

Other interactions potentially leading to increased tacrolimus blood levels
Tacrolimus is extensively bound to plasma proteins. Possible interactions with other medicinal products 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 the prokinetic agent metoclopramide, cimetidine and magnesium-aluminium-hydroxide.

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

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

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

BACK

Other interactions which have led 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, sulfamethoxazole + trimethoprim, 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.

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.

MAIN SIDE/ ADVERSE EFFECTS

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.

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).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Patients receiving immunosuppressive therapy are at increased risk of developing malignancies.

Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

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
Rare	Pericardial effusion
Very Rare	Echocardiogram abnormal, electrocardiogram QT prolonged, Torsades de Pointes
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	Pure red cell aplasia, agranulocytosis, haemolytic anaemia
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
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, acute and chronic pancreatitis, amylase increased, gastrooesophageal reflux disease, impaired gastric emptying
Rare	Subileus, pancreatic pseudocyst
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
Skin and subcutaneous tissue 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 spasms, pain in extremity*, back pain
Uncommon	Joint disorders
Rare	Mobility decreased
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, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities
Uncommon	Dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia
Vascular disorders	
Very Common	Hypertension
Common	Haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
Uncommon	Infarction, venous thrombosis deep limb, shock
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, ulcer
Very Rare	Fat tissue increased
Not Known	Febrile neutropenia
Immune system disorders	
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus.	
Hepatobiliary disorders	
Common	Hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
Rare	Hepatitic artery thrombosis, venoocclusive liver disease
Very Rare	Hepatic failure, bile duct stenosis
Reproductive system and breast disorders	
Uncommon	Dysmenorrhoea and uterine bleeding
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

*In isolated cases, pain in extremity has been reported as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS), which typically presents bilateral and symmetrical, severe, ascending pain in the lower extremities

OVERDOSE AND TREATMENT

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 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.

DOSAGE AND ADMINISTRATION

Tacrolimus therapy requires careful monitoring by adequately qualified and equipped personnel. The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. For patients with lupus nephritis, this product should be prescribed by physicians experienced in lupus nephritis therapy.

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

Dosing should commence orally, if necessary via an intranasal gastric tube. If the clinical condition of the patient does not allow oral therapy, initial intravenous dosing may be necessary.

Dosage Level Recommendations
Initial dose level recommendation.

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 of kidney transplant surgery.

If clinical condition of the patient does not allow oral dosing, then intravenous tacrolimus therapy should be initiated as a continuous 24-hour infusion at 0.01 to 0.05 mg/kg for liver transplant and 0.05 to 0.10 mg/kg for kidney transplant.

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. If the dose cannot be given orally, an initial intravenous dose of 0.05 mg/kg/day for liver transplantation or 0.1 mg/kg/day for kidney transplantation should be administered as a continuous 24-hour infusion.

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.

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. 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.

Patients should be converted from intravenous to oral medication as soon as individual circumstances permit. Intravenous therapy should not be continued for more than 7 days.

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. Trough blood levels of tacrolimus should also be monitored periodically during maintenance therapy. The frequency of blood level monitoring should be based on clinical need. 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.

Only for Tacrolimus Capsules 0.5mg and 1mg
Lupus nephritis: For adults, usually, a dose of 3mg as tacrolimus is orally administered, once daily after supper.

In order to avoid the development of adverse reactions in patients with lupus nephritis, it is recommended that the blood levels should be monitored monthly for 3 months after the start of tacrolimus therapy; thereafter, the blood levels approximately 12 hours after the administration should be monitored periodically, and the dosage should be adjusted. If this product does not improve the clinical signs of nephritis, such as urinary protein excretion, or the immunological findings after continuous treatment for 2 months or more, the treatment with this product should be discontinued, or the patient should be switched to another product. In cases where this product is sufficiently effective, it is recommended that the dose should be reduced to a level at which the effect can be maintained.

Special Population
Patient with Liver Impairment
A dose reduction is necessary.

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

Elderly Patients
Limited experience suggests that doses should be the same as for adults.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage	: Store below 30°C. Protect from light and moisture.
Presentation/ Packing	: Blister pack of 6x10's.
Manufactured for / Product Registration Holder (Malaysia) / Product Owner	: HOVID Berhad 121, Jalan Tunku Abdul Rahman (Jalan Kuala Kangsar), 30010 Ipoh, Perak, Malaysia.
Manufactured by	: Concord Biotech Limited 297-298/2p, Siyawada, Valthera, Ahmedabad, Gujarat 382225, India.
Date of revision	: October 2022

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