Proposed Professional Information for Medicines for Human Use:

GRAVTELL 0,5 mg, 1 mg, 5 mg

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GRAVTELL 0,5 mg hard gelatin capsules

GRAVTELL 1 mg hard gelatin capsules

GRAVTELL 5 mg hard gelatin capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GRAVTELL 0,5: Each hard capsule contains 0,5 mg tacrolimus.

GRAVTELL 1: Each hard capsule contains 1 mg tacrolimus.

GRAVTELL 5: Each hard capsule contains 5 mg tacrolimus.

Contains sugar: Lactose anhydrous

GRAVTELL 0,5: Each hard gelatin capsule contains 120,820 mg lactose anhydrous.

GRAVTELL 1: Each hard gelatin capsule contains 120,320 mg lactose anhydrous.

GRAVTELL 5: Each hard gelatin capsule contains 116,320 mg lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

GRAVTELL 0,5:

Light yellow hard gelatin capsules, size “4” imprinted with “TCR” on cap & “ABZ 0.5” on body containing white to off white granular powder.

GRAVTELL 1:

White hard gelatin capsules, size “4” imprinted with “TCR” on cap & “ABZ 1” on body containing white to off white granular powder.

GRAVTELL 5:

Pink hard gelatin capsules, size “4” imprinted with “TCR” on cap & “ABZ 5” on body containing white to off white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GRAVTELL is indicated for primary immunosuppression in liver and kidney allograft recipients and liver, kidney or heart allograft rejection resistant to conventional immunosuppressive regimens.

4.2 Posology and method of administration

Posology

Inadvertent, unintentional or unsupervised switching between Immediate and prolonged release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including under or over-immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulations or regimen should only take place under the close supervision of a transplant specialist. Following conversion to any alternative formulation, therapeutic medicine monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Absorption of orally administered tacrolimus in the immediate post-operative period in heart transplant patients is problematic and creates difficulties in designing a suitable dosing regimen. Therefore initiation of tacrolimus therapy via the intravenous route and conversion to oral dosing, when possible, or initiating GRAVTELL orally following antibody induction therapy are the two preferable options for use of GRAVTELL in heart transplant patients.

General statement

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

If the clinical condition of the patient allows oral dosing, administration of oral tacrolimus, as in GRAVTELL, should start as soon as practicable. In some liver transplantation patients, therapy has commenced orally by administering the capsule contents suspended in water via an intranasal gastric tube.

GRAVTELL is normally administered together with other immunosuppressive medicines. In isolated cases, successful maintenance therapy with GRAVTELL alone has also been described. GRAVTELL should not be given together with ciclosporin (see section 4.3). If allograft rejection or adverse events occur, alteration in the immunosuppressive regimen should be considered.

Mode of intake

It is recommended that the oral daily dose should be taken in two divided doses. The capsules should be swallowed with fluid, preferably water. Based on pharmacokinetic considerations, the capsules should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal to achieve maximal absorption (see section 4.5).

The capsules should be taken out of the blister only immediately before intake. After opening the aluminium wrapper, the capsules from the blisters must be used within 12 months. Patients should be cautioned not to swallow the desiccant contained within the aluminium wrapper.

Duration and onset of intake

To suppress graft rejection, the capsules normally have to be taken continuously. Therefore, no limitation of duration can be given.

Maintenance therapy in liver and kidney transplant recipients (adults and children) –

General considerations

Continuous immunosuppression with GRAVTELL is recommended to maintain graft survival. If progression of disease occurs (e.g. signs of acute rejection), alteration of the immunosuppressive regimen should be considered. Increase in the amount of corticosteroids, introduction of short courses of monoclonal antibodies and increase in the dose of GRAVTELL have all been used to manage rejection episodes.

If signs of toxicity are noted, the dose of GRAVTELL should be reduced. Patients should be instructed not to decrease the dose without the consent of the treating medical practitioner.

During the course of the post-transplant improvement of the patient, it is likely that the pharmacokinetics of tacrolimus may be altered, requiring adjustment of the dose.

Primary immunosuppression - adult patients

Liver transplantation

Initially, an oral dose in a range from 0,10 to 0,20 mg/kg/day should be administered in two divided doses. Initial oral doses have been administered in a range from 0,02 to 0,30 mg/kg/day

Kidney transplantation

Initially, an oral dose in a range from 0,15 to 0,40 mg/kg/day should be administered in two divided doses. If the clinical condition of the patient does not allow for oral dosing, then an initial intravenous dose of 0,05 to 0,10 mg/kg/24 h should be administered as a continuous infusion within the first 24 hours after the completion of surgery. Patients should be converted from intravenous to oral medication as soon as the individual circumstances permit.

Primary immunosuppression dose levels – paediatric patients

Paediatric patients generally require doses 1½ to 2 times higher than the recommended adult doses to achieve the same blood levels. Experience with initial oral administration in paediatric patients is limited.

Liver and kidney transplantation

An initial dose of 0,30 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 0,10 mg/kg/day for kidney transplantation should be administered as a continuous 24-hour infusion.

Maintenance therapy with GRAVTELL in liver or kidney transplant recipients

It is necessary to continue immunosuppression with oral GRAVTELL to maintain graft survival. Dosage recommendations should be based on individual patient experience. There is a trend towards the use of lower doses of GRAVTELL during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability.

Rescue therapy with GRAVTELL

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

The combined administration of ciclosporin and GRAVTELL is not recommended as GRAVTELL may increase the half-life of ciclosporin and exacerbate any toxic effects (see Section 4.3).
Therefore, care should be taken when converting patients from ciclosporin- to tacrolimus-based therapy. It is recommended that ciclosporin blood levels are monitored prior to the administration of GRAVTELL. The most appropriate time to initiate tacrolimus therapy should be based upon information on ciclosporin blood levels and the clinical condition of the patient. Dosing may be delayed in the presence of elevated ciclosporin levels e.g. in patients experiencing renal failure. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin may be affected.

Heart allograft rejection

An initial oral dose of 0,30 mg/kg/day should be administered in two divided doses (e.g. morning and evening). If the clinical condition of the patient prevents oral administration, an intravenous dose of 0,05 mg/kg/day should be administered as a continuous 24-hour infusion.

Special populations

Patients with liver impairment

A dose reduction may be necessary in patients with pre- and/or post-operative impairment, e.g. early graft dysfunction.

Patients with kidney impairment

No adjustment in dose is regarded as necessary on pharmacokinetic principles. However, careful monitoring of renal function, including serial creatinine estimations, calculations of creatinine clearance and monitoring of urine output, is recommended.

Race

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

Elderly patients

There Is no evidence presently available to suggest that doses should be altered in elderly patients.

Paediatric patients

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

Conversion from ciclosporin to GRAVTELL

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. GRAVTELL therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, GRAVTELL therapy has been initiated 12 to 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Various assays have been used to measure blood or plasma levels of tacrolimus, as contained in GRAVTELL. Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially

interacting medicines and the post transplant time interval. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Whole blood specimens should be collected into tubes containing ethylene diamine tetra acetic acid (EDTA) anticoagulant. Heparin anticoagulation is not recommended because of the tendency to form clots on storage. Samples that are not analysed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they should be deep frozen at -20 ºC for up to 12 months.

GRAVTELL whole blood trough levels should be monitored periodically during maintenance therapy. The frequency of blood level monitoring should be based on clinical needs, but in general, because of its long half-life, it is unnecessary to measure blood levels on a daily basis. Medicine level monitoring (TDM) is recommended during the early post transplantation period, following dose adjustment, after switching from another immunosuppressive regimen, and following co-administration of medicines which are likely to lead to interactions.

Clinical experience suggests that the majority of patients can be successfully managed if the blood concentrations of GRAVTELL are maintained below 25 ng/mL. It is necessary to consider the clinical condition of the patient when interpreting whole blood level concentrations. If the blood levels are below the limit of quantification of the assay and the patient’s clinical condition is satisfactory, then the dose should not be adjusted.

4.3 Contraindications

- Known hypersensitivity to tacrolimus, the tacrolimus in GRAVTELL or other macrolides.
- Pregnancy and lactation (see sections 4.6).
- Known hypersensitivity to other ingredients of the capsules.

Austell Pharmaceuticals (Pty) Ltd, 54/34/0444-6, GRAVTELL 0,5 mg, 1 mg, 5 mg Hard gelatin capsules

- Oral contraceptives (as tacrolimus may alter the metabolism of oral contraceptives), other forms of contraception should be used.
- Concomitant administration of live attenuated vaccines.
- Concomitant administration with ciclosporin.
- Concomitant use with grapefruit juice.

4.4 Special warnings and precautions for use

Prolonged-release formulations of tacrolimus are not inter0changeable with immediate-release formulations of tacrolimus without careful monitoring and supervision by a transplant specialist.

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 (see sections 4.2 and 4.8).

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

Substances with potential for interaction

When substances with a potential for interaction (see section 4.5) - particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole,

telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampicin, rifabutin) – are being combined with tacrolimus, tacrolimus blood levels should be
monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Herbal preparations containing St. John's wort (Hypericum perforatum) or other herbal preparations should be avoided when taking GRAVTELL due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity (see section 4.5).

The combined administration of ciclosporin and tacrolimus is contraindicated (see section 4.3) and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.5).

High potassium intake or potassium-sparing diuretics should be avoided (see section 4.5).

Certain combinations of tacrolimus with medicines known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

Vaccination

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines is contraindicated (see section 4.3).

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 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 GRAVTELL 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, bradydysrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see section 4.5).

Lymphoproliferative disorders and malignancies

Patients treated with tacrolimus, as contained in GRAVTELL have been reported to develop Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (see section 4.8). Patients switched to GRAVTELL 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 GRAVTELL. 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 medicines, 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 (see section 4.8).

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.

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.

Infections including opportunistic infections

Patients treated with immunosuppressants, including GRAVTELL 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.

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: lactose intolerance

This medicine contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Metabolic interactions

Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of 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 (see sections 4.2 and 4.4).

Inhibitors of metabolism

Clinically the following substances have been shown to increase tacrolimus blood levels:
Strong interactions have been observed with antifungal medicines such as ketoconazole, fluconazole, itraconazole, voriconazole, and isavuconazole, 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), 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*.
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, norethisterone, quinidine, tamoxifen, troleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and concomitant use is therefore contraindicated (see section 4.3).

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 (see sections 4.2 and 4.4).

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

As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures (see also section 4.3).

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

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

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 which have led to clinically detrimental effects

Concurrent use of tacrolimus with medicine known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole + trimethoprim, NSAIDs, ganciclovir or acyclovir).

Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.

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

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided (see sections 4.3 and 4.4).

Austell Pharmaceuticals (Pty) Ltd, 54/34/0444-6, GRAVTELL 0,5 mg, 1 mg, 5 mg Hard gelatin capsules

4.6 Fertility, pregnancy and lactation

Pregnancy

GRAVTELL is contraindicated in pregnancy. In animal studies (rats and rabbits), GRAVTELL has been shown to be teratogenic at doses that also demonstrated maternal toxicity. Preclinical and human data show that GRAVTELL is able to cross the placenta. The possibility of pregnancy should therefore be excluded before initiating GRAVTELL therapy.

Breastfeeding

Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving GRAVTELL (see section 4.3).

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 GRAVTELL is administered in association with alcohol.

4.8 Undesirable effects

a) Summary of the safety profile

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

Many of the adverse drug reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse drug reactions compared with intravenous use

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with Tacrolimus.

Frequency estimate:

Frequent (≥ 1/100)

Less frequent (< 1/100)

Not known (cannot be estimated from the available data).

System Organ Class	**Frequency**		
	Frequent (include SmPC	**Less Frequent (include SmPC**	**Not known (include SmPC**

	Very Common side effects followed by Common side effects)	**Uncommon side effects followed by Rare side effects followed by Very rare side effects)**	**ADRs with Frequency not known/ unknown)**
Infections and infestations	Viral, Bacterial, Fungal, Protozoal Infection. Generalised and localised infections can occur		
Neoplasms benign, malignant and unspecified (including cysts and polyps)	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	Anaemia, Leukopenia, Thrombocytopenia, Leukocytosis, Red blood cell analyses abnormal	Coagulopathies, Abnormal Coagulation and Bleeding analyses, Pancytopenia, Neutropenia Thrombotic Thrombocytopenic Purpura,	Pure red cell aplasia, Agranulocytosis, Haemolytic anaemia

		Hypoprothrombinaemia, Thrombotic microangiopathy	
Immune system disorders	Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus		
Endocrine disorders		Hirsutism	
Metabolism and nutrition disorders	Hyperglycaemic conditions, Diabetes mellitus, Hyperkalaemia Hypomagnesaemia, Hypophosphataemia, Hypokalaemia, Hypocalcaemia, Hyponatraemia, Fluid overload, Hyperuricaemia, Appetite decreased, Metabolic acidoses, Hyperlipidaemia, Hypercholesterolaemia,	Dehydration, Hypoproteinaemia, Hyperphosphataemia, Hypoglycaemia	

	Hypertriglyceridaemia, Other electrolyte abnormalities		
Psychiatric disorders	Insomnia, Anxiety symptoms, Confusion and Disorientation, Depression, Depressed mood, Mood disorders and Disturbances, nightmare, hallucination, mental disorders	Psychotic disorder	
Nervous system disorders	Tremor, Headache, Seizures, Disturbances in consciousness, Paraesthesias and Dysaesthesias, Peripheral neuropathies, Dizziness, Writing impaired, nervous system disorders	Coma, Central nervous system haemorrhages and Cerebrovascular accidents, Paralysis and Paresis, Encephalopathy, Speech and language abnormalities, Amnesia, Hypertonia, Myasthenia	
Eye disorders	Blurred Vision, Photophobia, Eye disorders	Cataract, Blindness	Optic neuropathy

Ear and labyrinth disorders	Tinnitus	Hypoacusis, Deafness neurosensory, Hearing impaired	
Cardiac disorders	Ischaemic coronary artery disorders, Tachycardia	Pericardial effusion, *Torsades de Pointes,* Ventricular arrhythmias and Cardiac arrest, Heart failures, Cardiomyopathies, Ventricular hypertrophy, Supraventricular arrhythmias, Palpitations	
Vascular disorders	Hypertension, Haemorrhage, Thrombembolic and ischaemic events, Peripheral vascular disorders, Vascular hypotensive disorders	Infarction, Venous thrombosis deep limb, Shock	
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Parenchymal lung disorders, Pleural effusion, Pharyngitis, Cough, Nasal congestion and Inflammations	Respiratory failures, Respiratory tract disorders, Asthma, Acute respiratory distress syndrome	

Gastrointestinal disorders	Diarrhoea, Nausea, 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	Ileus paralytic, Acute and Chronic pancreatitis, Gastrooesophageal reflux disease, Impaired gastric emptying, Subileus, Pancreatic pseudocyst	
Hepatobiliary disorders	Cholestasis and Jaundice, Hepatocellular damage and Hepatitis, Cholangitis	Hepatitic artery thrombosis, Venoocclusive liver disease, hepatic failure, Bile duct stenosis	

Skin and subcutaneous tissue disorders	Pruritus, Rash, Alopecias, Acne, Sweating increased	Dermatitis, Photosensitivity, Toxic epidermal necrolysis (Lyell's syndrome), Stevens Johnson syndrome	
Musculoskeletal and connective tissue disorders	Arthralgia, Muscle spasms, Pain in extremity, Back pain	Joint disorders Mobility decreased	
Renal and urinary disorders	Renal failure, Renal failure acute, Oliguria, Renal tubular necrosis, Nephropathy toxic, Urinary abnormalities, Bladder and urethral symptoms.	Anuria, Haemolytic uraemic syndrome, Nephropathy, Cystitis haemorrhagic	
Reproductive system and breast disorders		Dysmenorrhoea and Uterine bleeding	
General disorders	Asthenic conditions, Febrile disorders, Body temperature perception disturbed	Multi-organ failure, Influenza like illness, Temperature intolerance, Chest pressure sensation, Feeling jittery,	

		Feeling abnormal, Thirst, Fall, Chest tightness, Ulcer, Fat tissue increased	
Investigations	Hepatic enzymes and Function abnormalities, Blood alkaline Phosphatase increased, Weight increased	Amylase increased, ECG investigations abnormal, Heart rate and Pulse investigations abnormal, Weight decreased, Blood lactate Dehydrogenase increased, Echocardiogram abnormal, Electrocardiogram QT prolonged	
Injury, poisoning and procedural complications	Primary graft dysfunction		

c. Description of selected adverse reactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Experience with overdosage is limited. Several cases of accidental overdosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen and elevated serum creatinine concentrations, and increase in alanine aminotransferase levels.

No specific antidote to GRAVTELL 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, the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class:

A.34 Other (Immuno-suppressive macrolide lactone)

Pharmacotherapeutic group: Immunosuppressants, calcineurin inhibitors,

ATC Code: L04AD02

Mechanism of action

Tacrolimus is an immunosuppressive agent with activity in both *in vitro* and *in vivo* experiments. Tacrolimus inhibits the formation of cytotoxic lymphocytes that 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 interleukin-2, -3 and γ- interferon and the expression of the interleukin-2 receptor. On the molecular level, the

effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP), which is also responsible for the intracellular accumulation of the compound.

5.2 Pharmacokinetic properties

Absorption

In the rat, the major site of absorption was identified as the upper gastrointestinal tract.

Absorption of tacrolimus is incomplete and highly variable following oral administration. After oral administration, tacrolimus is variably absorbed. Some patients achieve peak plasma concentrations within 0,5 hours to 3 hours, while in other patients it appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile.

The poor dissolution of tacrolimus in gastric fluids resulting from low aqueous solubility and alterations in gastric motility may be partially responsible for this observation.

In kidney allograft patients, single oral doses of 0,10; 0,15 and 0,2 mg/kg resulted in peak blood concentrations of 19,2; 24,2; and 47,9 ng/ mL., respectively. The times to reach peak concentration varied from 0,7 to 6 hours.

The mean bioavailability of tacrolimus capsules was estimated to be 21,8 % in liver transplant patients, 20,1 % in kidney transplant patients, 14,4 to 17,4 % in healthy subjects and 25 % in paediatric liver transplant patients.

In heart allograft recipients tacrolimus is absorbed with a mean time to peak concentration (tmax) of approximately 1,5 hours. The oral bioavailability of tacrolimus averages 20 %, however there is a high degree of patient variability in heart transplant patients.

The oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat content. There was a decrease in AUC (plasma 27 %, whole blood 35 %), Cmax (plasma 50 %, whole blood 57 %), and an increase in tmax (both plasma and whole blood
173 %). Both rate and extent of absorption were reduced when tacrolimus was given with food. Bile does not influence the absorption of tacrolimus, and therefore commencement of tacrolimus therapy with an oral dose and early conversion of liver transplant patients to oral therapy is possible.

Austell Pharmaceuticals (Pty) Ltd, 54/34/0444-6, GRAVTELL 0,5 mg, 1 mg, 5 mg Hard gelatin capsules

Distribution and elimination

Distribution of tacrolimus is extensive. It is highly bound to red blood cells and to plasma proteins. Following intravenous infusion of tacrolimus, peak plasma concentrations are reached at the end of the infusion. Concentration declines rapidly after the end of infusion indicating rapid distribution of the medicine outside the plasma compartment. Once distribution equilibrium is reached, tacrolimus concentrations decline at a slower rate, corresponding to the disposition of the medicine.

The pharmacokinetics of tacrolimus after intravenous infusion to transplant patients may be described by a two-compartment model. In kidney transplant patients, the increase in AUC and Cmax after single oral dose post-transplant was proportional to the increase in oral dose.

In liver transplant patients, the mean trough level concentrations of tacrolimus remained relatively stable up to 6 months post-transplant. Based on plasma level data in transplant patients, the apparent volume of distribution averaged 1342 l, suggesting extensive distribution of tacrolimus in the body. In liver transplant patients, the volume of distribution averaged 64,4 l based on whole blood concentrations (0,85 l /kg when normalised to body weight) and 1094,5 l based on the plasma concentrations (150,1 l /h or 2,0 l /h/kg when normalised to body weight).

Measurement of minimum blood or plasma levels, which were correlated with AUC, provided an accurate reflection of total tacrolimus exposure. Tacrolimus is highly bound to plasma proteins (> 98,8 %) in rat, dog, monkey and man. The whole blood/plasma ratio appears to be approximately 20:1 (volunteer studies). Tacrolimus binds strongly to erythrocytes. This effect is dependent on temperature, lower temperatures resulting in lower plasma concentrations.

After oral administration (0,15 mg/kg twice daily) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in most patients.

The half-life of tacrolimus is long and variable, and clearance low.

The average total body clearance amounts to approximately 30 mL/min/g (7 - 103 mL/min/kg).

In liver transplant patients, the total body clearance observed was 4,5 L /h (whole blood concentration) and 150,1 L /h or 2,0 L /h/kg when normalised to body weight (plasma concentrations).

The plasma half-life of tacrolimus ranges between 3,5 and 40,5 h in renal transplant patients, other references stating up to 50 h. In liver transplant patients, the elimination half-life based on the whole blood concentration

averaged 11,7 h (range 6,1 – 20,9 h) and based on the plasma concentration 6,5 h (range 2,7 – 13,3 h).

The renal clearance is less than 1 mL/ min. The metabolites of tacrolimus are primarily excreted via the bile.

The mean clearance after oral intake and volume of distribution averaged 0,21 ± 0,08 L /hr/kg and 2,4 ± 0,8 L /kg while t1/2 averaged 8,7 ± 3,5 hrs in heart transplant patients.

Metabolism and Biotransformation

Tacrolimus is metabolised in the liver, primarily by the cytochrome P450-3A4 family. 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. Only one of the inactive metabolites is present at low concentrations in the systemic circulation. Therefore, metabolites do not meaningfully contribute to the pharmacological activity of tacrolimus.

Excretion

Following intravenous and oral administration of 14C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2 % of the radioactivity was eliminated in the urine. Less than 1 % of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination:

bile being the principal route of elimination.

Characteristics in patients

Relationship between plasma/blood concentrations and therapeutic activity

Individual dose adjustment controlled by monitoring of tacrolimus levels in whole blood may be helpful to achieve optimal therapy.

Several immunoassays are available for determining tacrolimus concentrations in whole blood, including a fully automatic micro particle enzyme immunoassay (MEIA).

Variations with respect to confounding factors, age, polymorphism, metabolism and concomitant pathological situations (renal failure, hepatic insufficiency)

Based on limited clinical experience, the kinetic properties of tacrolimus are not altered in elderly patients.

Children require a higher dose of tacrolimus, approximately 1½ to 2 times higher than that recommended for adults, possibly owing to a higher metabolic turnover.

Patients with liver dysfunction

Patients with liver dysfunction tended to have higher tacrolimus concentrations (and correspondingly longer half-lives and smaller clearance values) compared with patients with normal liver function.

As tacrolimus is extensively metabolised by the liver, patients with impaired liver function should be carefully monitored, and dose adjustment may be necessary (see section 4.2).

Patients with kidney dysfunction

Since tacrolimus is nearly completely metabolised, highly lipid-soluble, and has a molecular weight of 822 g/mole, it is not expected to be dialysable. Also, less than 1 % of an administered intravenous dose is excreted in the urine. Therefore, changes to the dosing regimen from the pharmacokinetic point of view are not necessary in patients with renal

failure or in patients undergoing dialysis. However, dosage adjustment may be necessary in patients with evidence of medicine-induced impairment of kidney function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Hypromellose 6 cps

Lactose monohydrate

Croscarmellose Sodium

Magnesium stearate

Capsule shell:

Iron oxide yellow (GRAVTELL 0,5)

Iron oxide red (GRAVTELL 5)

Titanium dioxide

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove blisters from carton until required for use.

This medicine does not require any special storage conditions.

Austell Pharmaceuticals (Pty) Ltd, 54/34/0444-6, GRAVTELL 0,5 mg, 1 mg, 5 mg Hard gelatin capsules

6.5 Nature and contents of container

GRAVTELL is packed in Alu/Alu blisters and packed into cardboard cartons in pack sizes of 30's and 50's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

GRAVTELL 0,5 mg: 54/34/0444.

GRAVTELL 1 mg: 54/34/0445.

GRAVTELL 5 mg: 54/34/0446.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 September 2024.

10. DATE OF REVISION OF THE TEXT

Austell Pharmaceuticals (Pty) Ltd, 54/34/0444-6, GRAVTELL 0,5 mg, 1 mg, 5 mg Hard gelatin capsules