WARNINGS
Malignancies and serious infections: Increased risk for developing serious infections and malignancies with tacrolimus or other immunosuppressants that may lead to hospitalisation or death (see section 4.4)
Extended-release formulations of tacrolimus are not interchangeable with immediate release formulations of tacrolimus without careful monitoring and supervision by a transplant specialist.

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE
TALOMUNE 0,5 mg capsules
TALOMUNE 1 mg capsules
TALOMUNE 5 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
TALOMUNE 0,5 mg
Each capsule contains 0,5 mg tacrolimus monohydrate. Contains sugar: lactose monohydrate 60,50 mg per capsule.
TALOMUNE 1 mg
Each capsule contains 1 mg tacrolimus monohydrate. Contains sugar: lactose monohydrate 59,40 mg per capsule.
TALOMUNE 5 mg
Each capsule contains 5 mg tacrolimus monohydrate. Contains sugar: lactose monohydrate 131,20 mg per capsule.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules
TALOMUNE 0,5 mg: White to off white powder filled in size 5 hard gelatin capsules with red opaque cap and red opaque body printed SAL on cap and 720 on body.
TALOMUNE 1 mg: White to off white powder filled in size 5 hard gelatin capsules with green opaque cap and green opaque body printed SAL on cap and 721 on body.
TALOMUNE 5 mg: White to off white powder filled in size 4 hard gelatin capsules with teal opaque cap and teal opaque body printed SAL on cap and 722 on body.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
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 formulation 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 TALOMUNE orally following antibody induction therapy are the two preferable options for use of TALOMUNE in heart transplant patients.
General statement
The dosage recommendations given below are intended to act as a guideline. TALOMUNE doses should be adjusted according to individual patient requirements. If the clinical condition of the patient allows oral dosing, administration of oral TALOMUNE 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. TALOMUNE is normally administered together with other immunosuppressive medicine. In isolated cases, successful maintenance therapy with TALOMUNE alone has also been described. TALOMUNE 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.
Duration and onset of intake
For onset of treatment see above. 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 TALOMUNE 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 TALOMUNE have all been used to manage rejection episodes. If signs of toxicity are noted, the dose of TALOMUNE 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 TALOMUNE may be altered, requiring adjustment of the TALOMUNE dose.
Primary immunosuppression - adult patients
Liver transplantation
Patients should be converted from intravenous to oral medication as soon as the individual circumstances permit.
Oral administration
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
Initial administration
Initially, an oral dose in a range from 0,15 to 0,40 mg/kg/day should be administered in two divided doses.
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.
Maintenance therapy with TALOMUNE in liver or kidney transplant recipients
It is necessary to continue immunosuppression with TALOMUNE to maintain graft survival. Dosage recommendations should be based on individual patient experience (see introductory remarks above). There is a trend towards the use of lower doses of TALOMUNE during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability.
Rescue therapy with TALOMUNE
In patients experiencing rejection episodes that are unresponsive to conventional immunosuppressive therapy, TALOMUNE treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.
The combined administration of ciclosporin and TALOMUNE is not recommended as TALOMUNE may increase the half-life of ciclosporin and exacerbate any toxic effects (see section 4.5). Therefore, care should be taken when converting patients from ciclosporin to TALOMUNE-based therapy. It is recommended that ciclosporin blood levels are monitored prior to the administration of TALOMUNE. The most appropriate time to initiate TALOMUNE 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).

DOSAGE ADJUSTMENTS IN SPECIFIC PATIENT 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 renal 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.

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 TALOMUNE in children under 18 years of age have not been established. Limited data are available but no recommendation on a dosage can be made.

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

Whole blood concentration monitoring
Various assays have been used to measure blood or plasma levels of TALOMUNE. 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 lubes 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 lie kept longer, they should be deep frozen at -20 °C tor up to 12 months, TALOMUNE 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 (therapeutic outcomes monitoring - TOM) 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 TALOMUNE 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.

Method of administration
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 sections 4.4 and 5.2). 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.

4.3 Contraindications
- Hypersensitivity to tacrolimus, other macrolides or to any of the excipients (see section 6.1)
- Pregnancy and lactation (see section 4.6).
- As TALOMUNE 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. (see section 4.6).

4.4 Special warnings and precautions for use
Not interchangeable with extended-release tacrolimus products medication errors
Medication errors, including substitution and dispensing errors, between tacrolimus immediate release products and tacrolimus extended-release products were reported. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under-or overexposure to tacrolimus. Tacrolimus is not interchangeable or substitutable for tacrolimus extended-release products. (see Boxed Warning). Changes between tacrolimus immediate release and extended-release dosage forms must occur under physician supervision. Instruct patients and caregivers to recognize the appearance of tacrolimus dosage forms (see section 2) and to confirm with the healthcare provider if a different medicine is dispensed. TALOMUNE therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources. TALOMUNE should only be prescribed and changes in immunosuppressive therapy, should only be initiated by medical practitioners experienced in immunosuppressive therapy and the management of transplant patients. The medical practitioner responsible for maintenance therapy should have complete information requisite for the follow-up of the patient. Dose and/or blood level adjustment, should only be undertaken by the transplant centre responsible for the transplant patient. Patients should be thoroughly controlled. In particular, during the first months post-transplant, close monitoring of the patient is required. TALOMUNE is not recommended for use in children below 18 years due to limited data on safety and/or efficacy. Herbal preparations containing St. John's Wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking TALOMUNE 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 (see section 4.5). High potassium intake or potassium-sparing diuretics should be avoided (see section 4.5). Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of TALOMUNE concentrations are recommended during episodes of diarrhoea.
Lymphoma and other malignancies
Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see Boxed Warning). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific medicine. As usual for patients with increased risk for skin cancer, examine patients for skin changes; exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen with a high protection factor. Post-transplant lymphoproliferative disorder (PTLD) has been reported in immunosuppressed organ transplant recipients. The majority of PTLD events appear related to Epstein-Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children. Monitor EBV serology during treatment.

Serious infections
Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Serious viral infections reported include:
- Polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection.
- JC virus-associated progressive multifocal leukoencephalopathy (PML).
- Cytomegalovirus infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor disease are at higher risk of developing CMV viremia and CMV disease.

Monitor for the development of infection and adjust the immunosuppressive regimen to balance the risk of rejection with the risk of infection (see section 4.8).
Tuberculosis must be excluded prior to TALOMUNE treatment.
New onset diabetes after transplant
Tacrolimus was shown to cause new onset diabetes mellitus in clinical trials of kidney, liver, and heart transplantation. New onset diabetes after transplantation may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk. Blood glucose concentrations should be monitored closely in patients using TALOMUNE (see section 4.8).
Nephrotoxicity
Tacrolimus, like other calcineurin inhibitors, can cause acute or chronic nephrotoxicity. Nephrotoxicity was reported in clinical trials (see section 4.8). Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range. The risk for nephrotoxicity may increase when tacrolimus is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or medicines associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors) (see section 4.5). Monitor renal function and consider dosage reduction if nephrotoxicity occurs.
Neurotoxicity
Tacrolimus may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremors, paraesthesia, headache, mental status changes, and changes in motor and sensory functions (see section 4.8). As symptoms may be associated with tacrolimus whole blood trough concentrations at or above the recommended range, monitor for neurologic symptoms and consider dosage reduction or discontinuation of TALOMUNE if neurotoxicity occurs.
Hyperkalaemia
Hyperkalaemia has been reported with tacrolimus use. Serum potassium levels should be monitored. Careful consideration should be given prior to use of other medicine also associated with hyperkalaemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) during tacrolimus therapy (see section 4.8). Monitor serum potassium levels periodically during treatment.
Hypertension
Hypertension is a frequent adverse effect of tacrolimus therapy and may require antihypertensive therapy (see section 4.8). The control of blood pressure can be accomplished with any of the common antihypertensive medicine, though careful consideration should be given prior to use of antihypertensive medicine associated with hyperkalaemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) (see section 4.4). Calcium-channel blocking medicine may increase tacrolimus blood concentrations and therefore require dosage reduction of TALOMUNE (see section 4.5).
Not recommended for use with sirolimus
TALOMUNE is not recommended for use with sirolimus:
- The use of sirolimus with tacrolimus in studies of de novo liver transplant patients was associated with an excess mortality, graft loss, and hepatic artery thrombosis (HAT) and is not recommended.
- The use of sirolimus (2 mg per day) with tacrolimus in heart transplant patients was associated with increased risk of renal function impairment, wound healing complications, and insulin-dependent post-transplant diabetes mellitus, and is not recommended.

Interactions with CYP3A4 Inhibitors and Inducers
When co-administering tacrolimus with strong CYP3A4 inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin), adjustments in the dosing regimen of tacrolimus and subsequent frequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions.
QT prolongation
Tacrolimus may prolong the QT/QTc interval and may cause *Torsade de Pointes*. Avoid tacrolimus in patients with congenital long QT syndrome. In patients with congestive heart failure, bradydysrhythmias, those taking certain antidysrhythmic medications or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnaesemia, consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment. When co-administering tacrolimus with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval, a reduction in tacrolimus dose, frequent monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of tacrolimus with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation (see section 4.5).
Myocardial hypertrophy
Myocardial hypertrophy has been reported in infants, children, and adults, particularly those with high tacrolimus trough concentrations, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving tacrolimus therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of TALOMUNE should be considered (see section 4.8).
Immunisations
Whenever possible, administer the complete complement of vaccines before transplantation and treatment with TALOMUNE. The use of live vaccines should be avoided during treatment with TALOMUNE; examples include (not limited to) the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines. Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with TALOMUNE.
Pure red cell aplasia
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. A mechanism for tacrolimus induced PRCA has not been elucidated. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of TALOMUNE should be considered (see section 4.8).
Contains lactose monohydrate
TALOMUNE contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance total lactase deficiency, glucose-galactose malabsorption should not take TALOMUNE.

4.5 Interaction with other medicines and other forms of interaction
Mycophenolic acid
When tacrolimus is prescribed with a given dose of a mycophenolic acid (MPA), exposure to MPA is higher with tacrolimus co-administration with MPA than with ciclosporin co-administration because ciclosporin interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA associated adverse reactions and reduce the dose of concomitantly administered mycophenolic acid medicines as needed.

Effect of other medicines on tacrolimus
Table 1 displays the effects of other medicines on tacrolimus
Table 1: Effects of Other Medicines /Substances on Tacrolimus *

Medicine/substance class or name	Interaction effect	Recommendations
Grapefruit or grapefruit juice†	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) (see section 4.4).	Avoid grapefruit or grapefruit juice.
Strong CYP3A inducers‡: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenobarbitone), St John's Wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection (see section 4.4).	Increase tacrolimus dose and monitor tacrolimus whole blood trough concentrations (see section 4.2).
Strong CYP3A inhibitors‡: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone, S*chisandra sphenanthera* extracts.	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) (see section 4.4).	Reduce tacrolimus dose (or give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations (see section 4.2).
Mild or moderate CYP3A Inhibitors: Clotrimazole, antibiotics (e.g., erythromycin, fluconazole), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl oestradiol, cimetidine, lansoprazole, and omeprazole.	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) (see section 4.4).	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed (see section 4.2).
Other medicines, such as: Magnesium and aluminium hydroxide antacids, metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) (see section 4.4).	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed (see section 4.2).
Mild or moderate CYP3A inducers, methylprednisolone, prednisone	May decrease tacrolimus concentrations.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed (see section 4.2).

*Tacrolimus dosage adjustment recommendation based on observed effect of co-administered medicine on tacrolimus exposures, literature reports of altered tacrolimus exposures, or the other medicine's known CYP3A inhibitor/inducer status.
†High dose or double strength grapefruit juice is a strong CYP3A inhibitor; low dose or single strength grapefruit juice is a moderate CYP3A inhibitor.
‡Strong CYP3A inhibitor/inducer, based on reported effect on exposures to tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on medicine-medicine interaction studies with midazolam (sensitive CYP3A probe substrate).

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.

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.

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

4.6 Fertility, pregnancy and lactation
Pregnancy
TALOMUNE is contraindicated in pregnancy (see section 4.3). In animal studies (rats and rabbits), tacrolimus has been shown to be teratogenic at doses that also demonstrated maternal toxicity. Preclinical and human data show that tacrolimus is able to cross the placenta. The possibility of pregnancy should therefore be excluded before initiating TALOMUNE therapy.
Breastfeeding
Preclinical data in rats suggest that tacrolimus is excreted into breast milk. Human data on effects of tacrolimus during the lactation period are limited. As detrimental effects on the newborn cannot be excluded, women should not breastfeed whilst receiving TALOMUNE.
Fertility
A negative effect of TALOMUNE 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
TALOMUNE is associated with visual and neurological disturbances. Patients treated with TALOMUNE who are affected by such disorders should not drive a car or operate dangerous machines. This effect may be enhanced when TALOMUNE is given together with alcohol.

4.8 Undesirable effects
a. Summary of the safety profile
The adverse event profile associated with immunosuppressive medicine is often difficult to establish owing to the underlying disease and the concurrent use of multiple medicines. There is evidence that some of the events stated below are reversible and respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse events compared with intravenous use.

b. Tabulated summary of adverse reactions
The following adverse reactions were reported during clinical studies and/or post-marketing use:

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequent	Increased risk tor infections (viral, bacterial,mycobacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur (see section 4.4)
	Frequency unknown	Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal; -polyoma virus-associated nephropathy, (PVAN) including graft loss (see section 4.4)
Neoplasms: benign malignant and unspecified (incl. cysts and polyps)	Less frequent	Increased risk of developing malignancies. Benign as well as malignant neoplasms including Epstein-Barr Virus (EBV)-associated lymphoproliferative disorders and skin malignancies (see section 4.4) have been reported
Blood and lymphatic system disorders	Frequent	Anaemia, leukopenia, thrombocylopenia, leukocytosis, abnormal red blood cell analyses
	Less frequent	Coagulopathies, abnormal coagulation and bleeding analyses, pancytopenia, neutropenia, thrombotic thrombocytopenic purpura, hypoprothrombinaemia (see section 4.4)
	Frequency unknown	Agranulocytosis, disseminated intravascular coagulation, haemolytic anaemia, pure red cell aplasia (see section 4.4)
Immune system disorders	Less frequent	Allergic and anaphylactoid reactions
Endocrine disorders	Less frequent	Hirsutism
Metabolism and nutrition disorders	Frequent	Hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, decreased appetite, anorexia, metabolic acidosis, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities
	Less frequent	Dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia
	Frequency unknown	Glycosuria, increased amylase including pancreatitis, weight decreased
Psychiatric disorders	Frequent	Insomnia, anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
	Less frequent	Psychotic disorder
Nervous system disorders	Frequent	Tremor, headache, seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, impaired writing, nervous system disorders
	Less frequent	Coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia, hypertonia, myasthenia
	Frequency unknown	Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopathy syndrome (PRES) (see section 4.4), progressive multifocal leukoencephalopathy (PML) (see section 4.4), quadriplegia, syncope
Eye disorders	Frequent	Blurred vision, pholophobia, eye disorders
	Less frequent	Cataract, blindness
Ear and labyrinth disorders	Frequent	Tinnitus
	Less frequent	Hypoacusis, neurosensory deafness, impaired hearing
Cardiac disorders	Frequent	Ischaemic coronary artery disorders, tachycardia
	Less frequent	Ventricular dysrhythmias and cardiac arrest, heart failure, cardiomyopathies, ventricular hypertrophy, supraventricular dysrhythmias, palpitations, abnormal ECG investigations, abnormal heart rate and pulse investigations; pericardial effusion, abnormal echocardiogram
	Frequency unknown	Atrial fibrillation, atrial flutter, electrocardiogram T wave abnormal, flushing, pericardial effusion, QT prolongation, Torsade de Pointes, ventricular extrasystoles, ventricular fibrillation (see section 4.4)
Vascular disorders	Frequent	Hypertension, haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
	Less frequent	Myocardial infarction, deep vein thrombosis shock, myocardial ischaemia, myocardial hypertrophy
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammation
	Less frequent	Respiratory failure, acute respiratory distress syndrome, respiratory tract disorders, asthma
	Frequency unknown	Interstitial lung disease, lung infiltration
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms, stomatitis and ulceration
	Less frequent	Paralytic ileus, peritonitis, acute and chronic pancreatitis, increased blood amylase, gastro-oesophageal reflux disease, impaired gastric emptying, subileus, pancreatic pseudocyst
	Frequency unknown	Colitis, enterocolitis, gastroenteritis, pancreatitis haemorrhagic, pancreatitis necrotising
Hepato-biliary disorders	Frequent	Hepatic enzymes and function abnormalities, cholestasis and jaundice, heptocellular damage and hepatitis, cholangitis
	Less frequent	Hepatic artery thrombosis, veno-occlusive liver disease, hepatic failure, bile duct stenosis
	Frequency unknown	Hepatic cytolysis, hepatic necrosis, hepatotoxicity, liver fatty
Skin and subcutaneous tissue disorders	Frequent	Pruritus, rash, alopecia, acne, increased sweating
	Less frequent	Dermatitis, photosensitivity, toxic epidermal necrolysis (Lyell's syndrome), Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, muscle cramps, pain in limb, back pain
	Less frequent	Joint disorders
	Frequency unknown	Pain in extremity including Calcineurin-Inhibitor Induced Pain Syndrome (CIPS).
Renal and urinary disorders	Frequent	Acute renal failure, renal impairment, renal failure, oliguria, renal tubular necrosis, toxic nephropathy, urinary abnormalities, bladder and urethral symptoms
	Less frequent	Haemolytic uraemic syndrome, haemorrhagic cystitis, nephropathy, anuria
Reproductive system and breast disorders	Less frequent	Dysmenorrhoea and uterine bleeding
General disorders and administration site conditions	Frequent	Disturbed body temperature perception, asthenic conditions, febrile disorders, oedema, pain and discomfort, increased blood alkaline phosphatase, increased weight
	Less frequent	Feeling jittery, multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling abnormal, increased blood lactate dehydrogenase, decreased weight, thirst, fall, chest tightness, decreased mobility, ulcer, increased fat tissue
	Frequency unknown	Hot flushes
Investigations	Frequency unknown	Regular 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
Injury, poisoning and procedural complications	Frequent	Primary graft dysfunction, medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or extended-release tacrolimus formulations, have been observed (see 4.4).
	Frequency unknown	A number of associated cases of transplant rejection have been reported

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
Experience of overdosage is limited. Earlier clinical experience (when initial induction doses were 2 or 3 times greater than those currently recommended) suggested that symptoms of overdosage may include renal, neurological and cardiac disturbances, glucose intolerance, hypertension and electrolyte disorders (e.g., hyperkalaemia). Over-immunosuppression may increase the risk for severe infections. Liver function clearly influences all pre- and post-operative pharmacokinetic variables. Patients with failing liver grafts or those switched from other immunosuppressive therapy to TALOMUNE should be monitored carefully to avoid overdosage. No specific antidote to TALOMUNE therapy is available. If overdosage occurs general supportive measures and symptomatic treatment should be conducted. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that TALOMUNE will not be dialysable. In isolated patients with very high plasma concentrations of tacrolimus, haemofiltration and haemodiafiltration have been reported to considerably decrease the tacrolimus levels. In cases of oral intoxication, the use of absorbents (such as activated charcoal) may be helpful.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Calcineurin inhibitors ATC Code: L04AD02
Mechanism of action
Tacrolimus is an immunosuppressive medicine with activity in both *in vitro* and *in vivo* experiments. In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes that are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependant 8-cell proliferation, as well as the formation of lymphokines such as interteukin-2, -3 and y-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
General characteristics
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 rapidly absorbed in some patients with peak plasma concentrations reached 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. 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 (t_{max}) 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 %), C_{max} (plasma 50 %, whole blood 57 %), and an increase in t_{max} (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.
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 C_{max} 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 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 oral clearance and volume of distribution averaged 0,21 ± 0,08 l/h/kg and 2,4 ± 0,8 l/kg while $t_{1/2}$ averaged 8,7 ± 3,5 hrs in heart transplant patients.
Metabolism and biotransformation
Tacrolimus is widely 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. In systemic circulation only one of the inactive metabolites is present al low concentrations. Therefore, metabolites do not contribute to the pharmacological activity of tacrolimus.
Excretion
Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2 % of the radioactivity was eliminated in the urine. Less than 1 % of unchanged tacrolimus was detected in the urine and faeces indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.
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 preliminary 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.
Patients with kidney dysfunction
Since tacrolimus is nearly completely metabolised, highly lipid-soluble, and has a molecular weight of 822 g/mol, 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.

5.3 Preclinical safety data
Carcinogenesis
Carcinogenicity studies in male and female rats and mice showed no relationship of tumour incidence to tacrolimus dosage was found. (see Boxed Warning and section 4.4).
Mutagenesis
No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.
Impairment of fertility
Tacrolimus administered orally to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryo-lethality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryo-lethal effects were indicated by a higher rate of pre- and post-implantation loss and increased numbers of undelivered and nonviable pups. When administered at 2,6 to 6,9 times the clinical dose range based on body surface area, tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on oestrus cycles, parturition, pup viability, and pup malformations.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsule fill: Croscarmellose sodium, Hypromellose 2910, Lactose monohydrate, Magnesium stearate (E572).
Capsule shell: The 0,5 mg capsule shell contains, FD & C Blue 1 (E133), FD & C Red 40 (E129), gelatin and titanium dioxide (E171). The 1 mg capsule shell contains FD & C Blue 1 (E133), gelatin, iron oxide yellow (E172) and titanium dioxide (E171). The 5 mg capsule shell contains D & C Red 28, D & C Yellow 10 (E104), FD & C Blue 1, gelatin, and titanium dioxide (E171).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store at or below 25 °C. Store in the original package until required for use.
HDPE Bottles: Keep the bottle tightly closed.
Blisters: Do not remove blisters from carton until required for use.

6.5 Nature and contents of container
HDPE container: 30 or 100 capsules packed in a transparent, round 50 ml HDPE container closed with a white, opaque plastic cap.
Blister pack: 10 capsules packed in aluminium foil (PVC/PVDC) blisters. 10 of such blisters will be packed in a printed carton.
Pack size: 100 capsules.

6.6 Special precautions for disposal and other handling
No specific precautions applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION
STRIDES PHARMA SA (PTY) LTD
106 16th Road, Building 2, Midrand, South Africa, 1686.

8 REGISTRATION NUMBERS
TALOMUNE 0,5 mg 54/32.16/0811; 1 mg 54/32.16/0812; 5 mg 54/32.16/0813

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
The date on the registration certificate of the medicine.

10 DATE OF REVISION OF THE TEXT

WAARSKUWINGS
Kwaadaardighede en ernstige infeksies: Verhoogde risiko vir die ontwikkeling van ernstige infeksies en kwaadaardige siektes met takrolimus of ander immuunonderdrukkers wat tot hospitalisasie of dood toe kan lei (sien afdeling 4.4). Verlengde-vrystelling formulerings van takrolimus is nie verwisselbaar met onmiddellike vrystelling formulerings van takrolimus sonder die versigtige monitering en toesig deur 'n oorplantings-spesialis nie.

SKEDULERINGSTATUS S4

1 NAAM VAN DIE MEDISYNE
TALOMUNE 0,5 mg kapsules
TALOMUNE 1 mg kapsules
TALOMUNE 5 mg kapsules

2 KWALITATIEWE EN KWANTITATIEWE KOMPOSISIE
TALOMUNE 0,5 mg
Elke kapsule bevat 0,5 mg takrolimusmonohidraat. Bevat suiker: laktosemonohidraat 60,50 mg per kapsule.
TALOMUNE 1 mg
Elke kapsule bevat 1 mg takrolimusmonohidraat. Bevat suiker: laktosemonohidraat 59,40 mg per kapsule.
TALOMUNE 5 mg
Elke kapsule bevat 5 mg takrolimusmonohidraat. Bevat suiker: laktosemonohidraat 131,20 mg per kapsule.
Sien afdeling 6.1 vir 'n volledige lys hulpstowwe.

3 FARMASEUTIESE VORM
Kapsules
TALOMUNE 0,5 mg:
Wit tot afwit poeier gevul in grootte 5 harde gelatienkapsules met rooi ondeursigtige dop en rooi ondeursigtige romp, met SAL op die kapsuledop en 720 op die kapsuleromp gedruk.
TALOMUNE 1 mg:
Wit tot afwit poeier gevul in grootte 5 harde gelatienkapsule met groen ondeursigtige dop en groen ondeursigtige romp, met SAL op die kapsuledop en 721 op die kapsuleromp gedruk.
TALOMUNE 5 mg:
Wit tot afwit poeier gevul in grootte 4 harde gelatienkapsule met teal ondeursigtige dop en teal ondeursigtige romp, met SAL op die kapsuledop en 722 op die kapsuleromp gedruk.

4 KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
Primêre immuunonderdrukking in ontvangers van lewer- en nier-alloweefseloorplanting en lewer-, nier- of hart-alloweefseloorplanting verwerping weerstandig teen konvensionele immuunonderdrukkende regimes.

4.2 Posologie en metode van toediening
Posologie
Onbewuste, onopsetlike, of ongekontroleerde omskakeling tussen onmiddellike- en verlengde-vrystelling formulerings van takrolimus is onveilig. Dit kan lei tot oorplanting verwerping of verhoogde voorkoms van newe-effekte, insluitende onder- of oor-immuunonderdrukking, as gevolg van kliniese relevante verskille in sistemiese blootstelling aan takrolimus. Pasiënte moet op 'n enkele formulering van takrolimus gehou word, met die ooreenkomstige daaglikse doseringsregimen; veranderings in formulering of regimen moet slegs plaasvind onder die noukeurige toesig van 'n oorplantings spesialis. Na oorskakeling na enige ander formulering, moet terapeutiese medisyne monitering uitgevoer word en dosisaanpassings gemaak word om te verseker dat die sistemiese blootstelling aan takrolimus in stand gehou word. Absorpsie van takrolimus wat oraal toegedien is in die onmiddellike post-operatiewe tydperk in hartoorplantingspasiënte is problematies en veroorsaak moeilikhede in ontwikkeling van 'n paslike dosis regimen. Daarom is aanvang van takrolimus behandeling via die intraveneuse roete en omskakeling na orale dosering, waar moontlik, of aanvang van orale TALOMUNE na teenliggaam induksie behandeling, die twee verkieslike opsies vir die gebruik van TALOMUNE in hartoorplantingspasiënte.
Algemene stellings
Die dosisaanbevelings vir orale en intraveneuse toediening hieronder is bedoel om as 'n riglyn te dien. TALOMUNE dosisse moet volgens die behoeftes van die individuele pasiënt aangepas word. Indien die kliniese toestand van die pasiënt orale dosering toelaat, moet toediening van orale TALOMUNE so gou as prakties moontlik begin word. In sommige pasiënte met leweroorplantings het orale terapie begin deur die inhoud van die kapsule te suspendeer in water en toe te dien deur intranasale gastriese buis. TALOMUNE word normaalweg saam met ander immuunonderdrukkende middels toegedien. In enkele gevalle is suksesvolle instandhoudingsterapie met TALOMUNE alleen ook omskryf. TALOMUNE moet nie saam met siklosporien gegee word nie (sien afdeling 4.3). Indien alloweefseloorplanting verwerping of nadelige, reaksies voorkom, moet 'n verandering in die immuunonderdrukkingsregimen oorweeg word.
Duur en aanvang van inname
Sien bo vir aanvang van behandeling. Om oorplantingsweefsel verwerping te onderdruk, moet die kapsules normaalweg aaneenlopend geneem word. Daarom kan geen tydsduurbeperking gegee word nie.
Instandhoudingsterapie in ontvangers van lewer- of nieroorplantings (volwassenes en kinders)
Algemene oorwegings
Voortdurende immuunonderdrukking met TALOMUNE word aanbeveel om weefseloorplanting oorlewing te handhaaf. Indien progressie van die siekte voorkom (bv. tekens van akute verwerping), moet verandering van die immuunonderdrukkende regimen oorweeg word. Verhoging in die hoeveelhede kortikosteroïede, introduksie van kort kursusse van monoklonale teenliggame en verhoging in die dosis van TALOMUNE, is alles al gebruik om verwerpings episodes te beheer. Indien tekens van toksisiteit gemerk word, moet die dosis van TALOMUNE verminder word. Pasiente moet instruksie gegee word om nie die dosis te verminder sonder die goedkeuring van die geneesheer wat hul behandel nie. Gedurende die verloop van die post-oorplanting verbetering van die pasiënt, is dit waarskynlik dat die farmakokinetika van TALOMUNE kan verander, wat aanpassing van die TALOMUNE dosis sal vereis.
Primêre immuunonderdrukking – volwasse pasiënte
Leweroorplanting
Pasiënte moet van intraveneuse na orale medikasie oorgeskakel word sodra die individuele omstandighede dit toelaat.
Orale toediening
Aanvanklik moet 'n orale dosis in 'n gebied van 0, 10 tot 0,20 mg/kg/dag in twee verdeelde dosisse toegedien word. Aanvanklike orale dosisse in 'n gebied van 0,02 tot 0,30 mg/kg/dag is al toegedien.
Nieroorplanting
Aanvanklike toediening
Aanvanklik moet 'n orale dosis in 'n gebied van 0,15 tot 0,40 mg/kg/dag in twee verdeelde dosisse toegedien word.
Primêre immuunonderdrukking dosisvlakke – pediatriese pasiënte
Pediatriese pasiënte benodig oor die algemeen dosisse 1½ tot 2 keer hoër as die aanbevole volwasse dosis om dieselfde bloedvlakke te bereik. Ondervinding met aanvanklike orale toediening in pediatriese pasiënte is beperk.
Lewer- en nieroorplantings
Vir lewer- en nieroorplantings moet 'n aanvanklike dosis van 0,30 mg/kg/dag in twee verdeelde dosisse toegedien word.
Instandhoudingsterapie met TALOMUNE in ontvangers van lewer- of nieroorplantings
Dit is nodig om aan te hou met immuunonderdrukking met TALOMUNE om weefseloorplanting oorlewing in stand te hou. Dosisaanbevelings moet gebaseer wees op individuele pasiënt ondervindings (sien inleidende opmerkings hierbo). Daar is 'n neiging vir die gebruik van laer dosisse van TALOMUNE gedurende instandhoudingsterapie. Dosering moet primêr gebaseer word op kliniese assesserings van verwerping en draaglikheid.
Reddingsterapie met TALOMUNE
By pasiënte wat verwerpings episodes ondervind en nie op konvensionele immuunonderdrukkingsterapie reageer nie, moet TALOMUNE behandeling begin word met die aanvanklike dosis wat aanbeveel is vir primêre immuunonderdrukking in daardie spesifieke alloweefseloorplanting. Die gesamentlike toediening van siklosporien en TALOMUNE word nie aanbeveel nie, aangesien TALOMUNE die halfleeftyd van siklosporien kan verleng en toksiese effekte kan vererger (sien afdeling 4.5). Wees daarom versigtig wanneer pasiënte van siklosporien- na TALOMUNE-gebaseerde terapie oorgeskakel word. Dit word aanbeveel dat siklosporien bloedvlakke gemonitor word voor toediening van TALOMUNE. Die mees geskikte tyd om met TALOMUNE behandeling te begin, moet gebaseer word op inligting van siklosporien bloedvlakke en die kliniese toestand van die pasiënt. Dosering kan uitgestel word in teenwoordigheid van verhoogde siklosporien vlakke, bv. in pasiënte wat nierversaking opdoen. Monitering van die siklosporien bloedvlakke moet voortgesit word na oorskakeling omdat die opruiming van siklosporien beïnvloed kan word.
Hart-alloweefseloorplanting verwerping
'n Aanvanklik orale dosis van 0,30 mg/kg/dag moet toegedien word in twee verdeelde dosisse (bv. oggend en aand).

DOSISAANPASSINGS BY SPESIFIEKE PASIENTBEVOLKINGS
Pasiente met lewerbeskadiging
'n Dosisvermindering kan nodig wees by pasiënte met pre- en/of post-operatiewe beskadiging, bv. vroeë weefseloorplanting disfunksie.
Pasiente met nierbeskadiging
Geen dosisaanpassing word nodig geag op farmakokinetiese beginsels nie. Versigtige monitering van renale funksie, insluitende reeksgewyse bepaling van kreatinien, berekenings van kreatinienopruiming en monitering van urien uitset, word egter aanbeveel.
Bejaarde pasiënte
Daar is tans geen bewyse beskikbaar wat aandui dat dosisse in bejaarde pasiënte aangepas moet word nie.
Pediatriese pasiënte
Die veiligheid en doeltreffendheid van TALOMUNE by kinders jonger as 18 jaar is nog nie vasgestel nie. Beperkte data is beskikbaar, maar geen aanbeveling oor die dosis kan gemaak word nie.
Omskakeling van siklosporien na TALOMUNE
Sorg moet aan die dag gelê word wanneer pasiënte van siklosporien-gebaseerde na takrolimus-gebaseerde terapie oorgeskakel word. TALOMUNE terapie moet begin word nadat siklosporien bloedkonsentrasies en die kliniese toestand van die pasiënt in ag geneem is. Dosering moet uitgestel word in die teenwoordigheid van verhoogde siklosporien bloedvlakke. In die praktyk is TALOMUNE terapie 12 tot 24 uur na staking van siklosporien begin. Monitering van siklosporien bloedvlakke moet voortduur na die oorskakeling, aangesien die suiwering van siklosporien geaffekteer kan wees.
Monitering van heelbloedkonsentrasies
Verskeie analises is gebruik om TALOMUNE vlakke in bloed of plasma te meet. Monitering van takrolimus bloedkonsentrasies tesame met ander laboratorium en kliniese parameters word geag as 'n essensiële hulpmiddel tot pasiënt beheer vir die evaluering van verwerping, toksisiteit, dosisaanpassings en samewerking. Faktore wat die frekwensie van monitering beïnvloed sluit in, maar is nie beperk tot, hepatiese of renale disfunksie, die byvoeging of staking van potensiële interaktiewe geneesmiddels en post-oorplanting tydsverloop. Bloedkonsentrasie monitering is nie 'n plaasvervanger vir renale- en lewerfunksie monitering en weefsel biopsies nie. Heelbloed spesimens moet in buise versamel word wat etileendiamien-tetra-asetielsuur (EDTA) antikoagulant bevat. Heparien antikoagulasie word nie aanbeveel nie as gevolg van die neiging om klonte te vorm tydens berging. Monsters wat nie onmiddellik geanaliseer word nie, moet by kamer temperatuur of in 'n yskas gestoor word en moet binne 7 dae ontleed word; indien monsters langer gehou moet word, moet dit gediepvries word teen -20 ºC vir tot 12 maande. TALOMUNE heelbloed trogvlakke moet periodiek tydens instandhoudingsterapie gemonitor word. Die frekwensie van bloedvlak monitering moet op kliniese behoeftes gebaseer word, maar oor die algemeen is dit onnodig om bloedvlakke op 'n daaglikse basis te meet vanweë die lang halfleeftyd. Monitering van geneesmiddelvlakke (TDM) word aanbeveel in die tydperk kort na die oorplanting, na dosisaanpassing, na oorskakeling vanaf 'n ander immuunonderdrukkingsregimen en na gesamentlike toediening van geneesmiddels wat moontlik tot interaksies kan lei. Kliniese ondervinding toon dat die meeste pasiënte suksesvol beheer kan word indien die TALOMUNE bloedkonsentrasies onder 25 ng/ml gehou word. Dit is nodig om die kliniese toestand van die pasiënt in gedagte te hou wanneer die heelbloedkonsentrasies geïnterpreteer word. Indien die bloedvlakke onder die kwantifiseringslimiet van die toets is en die pasiënt se kliniese toestand bevredigend is, moet die dosis nie aangepas word nie.
Metode van toediening
Dit word aanbeveel dat die mondelikse daaglikse dosis in twee verdeelde dosisse geneem moet word. Die kapsules moet met vloeistof gesluk word, verkieslik water. Gebaseer op farmakokinetiese oorwegings, moet die kapsule op 'n leë maag of te minste 1 uur voor of 2 tot 3 ure na 'n maaltyd geneem word, om maksimale absorpsie te bereik (sien afdelings 4.4 en 5.2). Die kapsules moet slegs uit die stulpstrook verwyder word onmiddellik voor inname. Nadat die aluminium omhulsel oopgemaak is, moet die kapsules van die stulpstroke binne 12 maande gebruik word.

4.3 Kontra-indikasies
- Hipersensitiwiteit teenoor takrolimus, ander makroliede of teenoor enige van die onaktiewe bestanddele (sien afdeling 6.1)
- Swangerskap en borsvoeding (sien afdeling 4.6).
- Aangesien TALOMUNE die metabolisme van orale voorbehoedmiddels kan verander, moet ander maniere van voorbehoeding gebruik word.
- Gelyktydige toediening van lewende verswakte entstowwe.
- Gelyktydige toediening met siklosporien.
- Gelyktydige gebruik met pomelosap (sien afdeling 4.6).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Nie verwisselbaar met takrolimusprodukte met verlengde vrystelling medikasiefoute nie
Medikasiefoute, insluitend vervangings- en toedieningsfoute, tussen takrolimusprodukte met onmiddellike vrystelling en takrolimusprodukte met verlengde vrystelling is gerapporteer. Dit het gelei tot ernstige nadelige reaksies, insluitend oorplantingsweefsel verwerping, of ander nadelige reaksies as gevolg van onder- of oorblootstelling aan takrolimus. Takrolimus is nie verwisselbaar of vervangbaar vir takrolimusprodukte met verlengde vrystelling nie (sien Geboksde Waarskuwing). Veranderings tussen die onmiddellike vrystelling van takrolimus en doseervorme met verlengde vrystelling moet onder toesig van 'n dokter plaasvind. Beveel pasiënte en versorgers om die voorkoms van takrolimus-doseervorms te herken (sien afdeling 2) en om met die gesondheidsorgverskaffer te bevestig as 'n ander medisyne uitgedeel word. TALOMUNE-terapie vereis noukeurige monitering in eenhede wat toegerus is met voldoende laboratorium- en ondersteunende mediese hulpbronne. TALOMUNE moet slegs voorgeskryf word en veranderinge in immuunonderdrukkende terapie moet slegs begin word deur mediese praktisyns wat ondervinding het in immuunonderdrukkende terapie en die behandeling van oorplantingspasiënte. Die mediese praktisyn wat verantwoordelik is vir onderhoudsterapie, moet volledige inligting hê wat benodig word vir die opvolging van die pasiënt. Dosis- en/of bloedvlakaanpassing moet slegs gedoen word deur die oorplantingsentrum wat verantwoordelik is vir die oorplantingspasiënt. Pasiënte moet deeglik beheer word. In die besonder, gedurende die eerste maande na die oorplanting, is noukeurige monitering van die pasiënt nodig. TALOMUNE word nie aanbeveel vir gebruik vir kinders onder 18 jaar nie, vanweë die beperkte inligting oor veiligheid en/of doeltreffendheid. Kruiepreparate wat St John's Wort (*Hypericum perforatum*) bevat, of ander kruiemiddels, moet vermy word tydens die gebruik van TALOMUNE as gevolg van die risiko van interaksies wat lei tot afname in die bloedkonsentrasie van takrolimus en verminderde kliniese effek van takrolimus. Die gesamentlike toediening van siklosporien en takrolimus moet vermy word, en die toediening van takrolimus aan pasiënte wat voorheen siklosporien ontvang het moet met versigtigheid hanteer word (sien afdeling 4.5). 'n Hoë kaliuminname of kaliumsparende diuretika moet vermy word (sien afdeling 4.5). Aangesien die vlakke van takrolimus in bloed beduidend kan verander tydens episodes van diarree, word bykomende monitering van TALOMUNE-konsentrasies tydens episodes van diarree aanbeveel.
Limfoom en ander kwaadaardighede
Pasiënte wat immuunonderdrukkers ontvang, insluitend takrolimus, loop 'n verhoogde risiko om limfoom en ander kwaadaardige siektes te ontwikkel, veral in die vel (sien Geboksde Waarskuwing). Die risiko hou blykbaar verband met die intensiteit en duur van immuunonderdrukking eerder as met die gebruik van enige spesifieke medisyne. Soos gewoonlik vir pasiënte met 'n verhoogde risiko vir velkanker, ondersoek pasiënte vir velveranderings; blootstelling aan sonlig en UV-lig moet beperk word deur beskermende klere te dra en 'n breëspektrum sonskerm met 'n hoë beskermingsfaktor te gebruik. Post-oorplanting limfoproliferatiewe versteuring (PTLD) is gerapporteer by immuunonderdrukte orgaanoorplanting ontvangers. Die meerderheid PTLD-gebeure blyk verband te hou met Epstein-Barr Virus (EBV)-infeksie. Die risiko van PTLD kom die grootste voor by individue wat EBV-seronegatief is, 'n populasie wat baie jong kinders insluit. Monitor EBV serologie tydens behandeling.

Ernstige infeksies
Pasiënte wat immuunonderdrukkers ontvang, insluitend takrolimus, loop 'n groter risiko om bakteriële, virale, swam- en protosoïese-infeksies te ontwikkel, insluitend opportunistiese infeksies. Hierdie infeksies kan lei tot ernstige, insluitend noodlottige, uitkomste. Ernstige virusinfeksies wat gerapporteer is, sluit in:
- Polioomvirus-geassosieerde nefropatie (PVAN), meestal as gevolg van BK-virusinfeksie nefropatie.
- JC-virus geassosieerde progressiewe multifokale leuko-enkefalopatie (PML).
- Sitomegalovirusinfeksies: SMV-seronegatiewe oorplantingspasiënte wat 'n orgaan ontvang van 'n SMV-seropositiewe skenkersiekte, loop 'n hoër risiko om SMV-viremie en SMV-siekte te ontwikkel.

Monitor vir die ontwikkeling van infeksie en pas die immuunonderdrukkende regime aan om die risiko van verwerping met die risiko van infeksie te balanseer (sien afdeling 4.8).
Tuberkulose moet uitgesluit word voor behandeling met TALOMUNE.
Nuwe aanvang van diabetes na oorplanting
Daar is getoon dat takrolimus nuwe diabetes mellitus veroorsaak in kliniese proewe met nier-, lewer- en hartoorplanting. Nuwe aanvang van diabetes na oorplanting kan by sommige pasiënte omkeerbaar wees. Afro-Amerikaanse en Spaanse nieroorplantingspasiënte loop 'n verhoogde risiko. Bloedglukosekonsentrasies moet fyn dopgehou word by pasiënte wat TALOMUNE gebruik (sien afdeling 4.8).
Nefrotoksisiteit
Takrolimus, soos ander kalsineurinremmers, kan akute of chroniese nefrotoksisiteit veroorsaak. Nefrotoksisiteit is in kliniese toetse gerapporteer (sien afdeling 4.8). Oorweeg dosisverlaging by pasiënte met verhoogde serumkreatinien- en takrolimusvolbloedkonsentrasies groter as die aanbevole reeks. Die risiko vir nefrotoksisiteit kan verhoog wanneer takrolimus gelyktydig met CYP3A-remmers toegedien word (deur die konsentrasie van die volle bloed van takrolimus) of medisyne wat verband hou met nefrotoksisiteit (bv. aminoglikosiede, gansiklovir, amfoterisien B, sisplatien, nukleotied-omgekeerde transkriptase-remmers, protease-remmers) (sien afdeling 4.5). Monitor die nierfunksie en oorweeg die vermindering van dosis as nefrotoksisiteit voorkom.
Neurotoksisiteit
Takrolimus kan 'n spektrum van neurotoksisiteite veroorsaak. Die ernstigste neurotoksisiteite sluit in posterior omkeerbare ensefalopatie sindroom (PRES), delirium, stuipe en koma; ander sluit in bewing, parestesie, hoofpyn, veranderde geestestoestand en veranderinge in motoriese en sensoriese funksies (sien afdeling 4.8). Aangesien simptome geassosieer kan word met takrolimus volbloed trogkonsentrasies binne of hoër as die aanbevole reeks, monitor vir neurologiese simptome en oorweeg die vermindering van die dosis of staking van TALOMUNE indien neurotoksisiteit voorkom.
Hiperkalemie
Hiperkalemie is aangemeld met die gebruik van takrolimus. Die serumkaliumvlakke moet gemonitor word. Daar moet deeglik oorweeg word voordat ander medisyne gebruik word wat ook met hiperkalemie (bv. kaliumsparende diuretika, ACE-remmers, angiotensienreseptorblokkers) gepaard gaan tydens takrolimusbehandeling (sien afdeling 4.8). Monitor serumkaliumvlakke gereeld tydens behandeling.
Hipertensie
Hipertensie is 'n gereelde nadelige effek van takrolimusbehandeling en kan antihipertensiewe behandeling benodig (sien afdeling 4.8). Die bloeddrukbeheer kan met enige van die algemene antihipertensiewe medisyne verkry word, maar deeglike oorweging moet gegee word voordat die antihipertensiewe medisyne wat verband hou met hiperkalemie (bv. kaliumsparende diuretika, ACE-remmers, angiotensienreseptorblokkers) gebruik word (sien afdeling 4.4). Kalsiumkanaalblokkende medisyne kan takrolimus se bloedkonsentrasies verhoog en benodig dus dosisverlaging van TALOMUNE (sien afdeling 4.5).
Nie aanbeveel vir gebruik met sirolimus nie
TALOMUNE word nie aanbeveel vir gebruik saam met sirolimus nie:
- Die gebruik van sirolimus en takrolimus in studies van de novo-leweroorplantingspasiënte is geassosieer met 'n oormatige sterftes, entverlies en hepatiese trombose (HAT) en word nie aanbeveel nie.
- Die gebruik van sirolimus (2 mg per dag) saam met takrolimus by hartooplantingspasiënte het gepaard gegaan met 'n verhoogde risiko van nierfunksie inkorting, komplikasies in wondgenesing en insulien-afhanklike diabetes mellitus na die oorplanting, en word nie aanbeveel nie.

Interaksies met CYP3A4-inhibeerders en induseerders
By die gesamentlike toediening van takrolimus met sterk CYP3A4-inhibeerders (bv. telaprevir, boseprevir, ritonavir, ketokonasool, itrakonasool, vorikonasool, klaritromisien) en sterk induseerders (bv. rifampien, rifabutien), is aanpassings in die doseerregimen van takrolimus en daaropvolgende gereelde monitering van takrolimusvolbloedkonsentrasies en takrolimus-geassosieerde newe-reaksies nodig.
QT-verlenging
Takrolimus kan die QT/QTc interval verleng en kan *Torsade de Pointes* veroorsaak. Vermy takrolimus by pasiënte met aangebore lang QT-sindroom. By pasiënte met kongestiewe hartversaking, bradidisritmie, diegene wat sekere antidisritmiese medisyne of ander medisyne gebruik wat tot QT-verlenging lei, en diegene met elektrolietversteurings soos hipokalemie, hipokalsemie of hipomagnesemie, moet dit oorweeg word om elektrokardiogramme te neem en elektroliete periodiek te monitor tydens behandeling.
By die toediening van takrolimus met ander substrate en / of remmers van CYP3A4 wat ook die potensiaal het om die QT-interval te verleng, word 'n vermindering in die dosis van takrolimus, gereelde monitering van takrolimus volbloedkonsentrasies en monitering vir QT-verlenging aanbeveel. Daar is gerapporteer dat die gebruik van takrolimus met amiodaroon tot verhoogde takrolimus-volbloedkonsentrasies lei, met of sonder gelyktydige QT-verlenging (sien afdeling 4.5).
Miokardiale hipertrofie
Miokardiale hipertrofie was gerapporteer in babas, kinders en volwassenes, veral diegene met 'n hoë takrolimuskonsentrasie, en word gewoonlik deur eggokardiografiese gedemonstreerde konsentriese toenames in die linker ventrikulêre posteriorwand en interventrikulêre septum dikte gemanifesteer. Hierdie toestand lyk in die meeste gevalle omkeerbaar na dosisverlaging of staking van die behandeling. By pasiënte wat nierversaking of kliniese manifestasies van ventrikulêre disfunksie ontwikkel tydens takrolimusbehandeling, moet eggokardiografiese evaluering oorweeg word. As miokardiale hipertrofie gediagnoseer word, moet die dosisvermindering of staking van TALOMUNE oorweeg word (sien afdeling 4.8).
Inentings
Indien moontlik, moet die volledige aanvulling van entstowwe toegedien word voor oorplanting en behandeling met TALOMUNE. Die gebruik van lewende entstowwe moet vermy word tydens behandeling met TALOMUNE; voorbeelde sluit in (nie beperk tot) die volgende: intranasale griep, masels, pampoentjies, rubella, orale polio, BCG, geelkoors, varisella en TY21a-tifus-entstowwe. Gedeaktiveerde entstowwe wat veilig is vir toediening na oorplanting is moontlik nie immunogenies voldoende tydens behandeling met TALOMUNE nie.
Suiwer rooisel aplasie
Gevalle van suiwer rooisel aplasie (PRCA) is gerapporteer by pasiënte wat met takrolimus behandel is. 'n Meganisme vir takrolimus-geïnduseerde PRCA is nie toegelig nie. Alle pasiënte het risikofaktore vir PRCA gerapporteer, soos parvovirus B19-infeksie, onderliggende siekte of gepaardgaande medisyne wat verband hou met PRCA. As PRCA gediagnoseer word, moet staking van TALOMUNE oorweeg word (sien afdeling 4.8).
Bevat laktosemonohidraat
TALOMUNE bevat laktosemonohidraat wat 'n uitwerking op die glukemiese beheer van pasiënte met diabetes mellitus kan hê. Pasiënte met seldsame oorerflike toestande van galaktose-onverdraagsaamheid, totale laktase-tekort of glukose-galaktose wanabsorpsie, moet nie TALOMUNE gebruik nie.

4.5 Interaksie met ander medisyne en ander vorms van interaksie
Mikofenolsuur
Wanneer takrolimus voorgeskryf word met 'n gegewe dosis mikofenolsuur (MPA), is blootstelling aan MPA hoër by takrolimus-toediening met MPA as met siklosporientoediening, omdat siklosporien die enterohepatiese hersirkulasie van MPA onderbreek, terwyl takrolimus dit nie doen nie. Monitor vir MPA-geassosieerde newe-reaksies en verminder die dosis gelyktydige toegediende mikofenolsuurmedisyne soos nodig.
Effekte van ander medisyne op takrolimus
Tabel 1 vertoon die effekte van ander medisyne op takrolimus
Tabel 1: Effekte van Ander Medisyne/Middels op Takrolimus *

Medisyne/middel klas of naam	Interaksie effek	Aanbevelings
Pomelo of pomelosap †	Kan takrolimus volbloed trogkonsentrasies verhoog en die risiko van ernstige newe-reaksies verhoog (bv. neurotoksisiteit, QT-verlenging) (sien afdeling 4.4).	Vermy pomelo of pomelosap
Sterk CYP3A-induseerders ‡: Antimikobakterieë (bv. rifampien, rifabutien), antikonvulsante (bv. fenobarbitoon), St John's Wort	Kan takrolimus volbloed trogkonsentrasies verlaag en die risiko vir verwerping verhoog (sien afdeling 4.4).	Verhoog die dosis takrolimus en monitor takrolimus-volbloedtrogkonsentrasies (sien afdeling 4.2).
Sterk CYP3A-inhibeerders ‡: Protease-inhibeerders (bv. nelfinavir, telaprevir, boseprevir, ritonavir), asool anti-swam middels (bv. vorikonasool, posakonasool, itrakonasool, ketokonasool), antibiotika (bv. klaritromisien, troleandomisien, chlooramfenikol), nefasodoon, *Schisandra sphenanthera* ekstrakte.	Kan takrolimus volbloed trogkonsentrasies verhoog en die risiko van ernstige newe-reaksies verhoog (bv. neurotoksisiteit, QT-verlenging) (sien afdeling 4.4).	Verlaag takrolimus dosis (gee 'n derde van die oorspronklike dosis) en pas die dosis aan op grond van die takrolimus-volbloedtrogkonsentrasies (sien afdeling 4.2).
Swak of matige CYP3A-inhibeerders: Klotrimasool, antibiotika (bv. eritromisien, flukonasool), kalsiumkanaalblokkers (bv. verapamiel, diltiasem, nifedipien, nikardipien), amiodaroon, danasol, etinielestradiol, simetidien, lansoprasool en omeprasool	Kan takrolimus volbloed trogkonsentrasies verhoog en die risiko van ernstige newe-reaksies verhoog (bv. neurotoksisiteit, QT-verlenging) (sien afdeling 4.4).	Monitor die volbloedtrogkonsentrasies van takrolimus en verminder die dosis van takrolimus indien nodig (sien afdeling 4.2).
Ander medisyne, soos: Teensuurmiddels in magnesium en aluminium, metoklopramied	Kan takrolimus volbloed trogkonsentrasies verhoog en die risiko van ernstige newe-reaksies verhoog (bv. neurotoksisiteit, QT-verlenging) (sien afdeling 4.4).	Monitor die volbloedtrogkonsentrasies van takrolimus en verminder die dosis van takrolimus indien nodig (sien afdeling 4.2).
Swak of matige CYP3A-induseerders, metielprednisoloon, prednisoon	Kan takrolimus konsentrasies verlaag.	Monitor die volbloedtrogkonsentrasies van takrolimus en pas dosis van takrolimus indien nodig (sien afdeling 4.2).

*Aanbeveling van dosisaanpassing van Takrolimus gebaseer op die waargenome effek van medisyne wat toegedien word op takrolimus-blootstelling, literatuurverslae van veranderde takrolimus-blootstellings, of die bekende CYP3A-remmer/induseerstatus van die ander medisyne.
†Hoë dosis of dubbele sterkte pomelosap is 'n sterk CYP3A-inhibeerder; lae dosis of enkelsterkte pomelosap is 'n matige CYP3A-inhibeerder.
‡Sterk CYP3A-inhibeerder/-induseerder, gebaseer op gerapporteerde effek op blootstelling aan takrolimus, tesame met *in vitro*-CYP3A-inhibeerder/-induseerder ondersteunende data, of gebaseer op medisyne-interaksiestudies met midasolaam (sensitiewe CYP3A-sonde-substraat).
Daar is getoon dat takrolimus die bloedvlak van fenitoïen verhoog. Aangesien takrolimus die opklaring van steroïed-baseerde voorbehoedmiddels kan verminder wat tot verhoogde blootstelling aan hormone kan lei, moet daar veral opgelet word wanneer daar oor voorbehoedmaatreëls besluit word. Beperkte kennis van interaksies tussen takrolimus en statiene is beskikbaar. Kliniese data dui daarop dat die farmakokinetika van statiene grootliks onveranderd is deur die toediening van takrolimus.

Ander interaksies wat kliniese nadelige gevolge het
Gelyktydige gebruik van takrolimus met geneesmiddels waarvan bekend is dat dit nefrotoksiese of neurotoksiese effekte het, kan hierdie effekte verhoog (bv. aminoglikosiede, girase-inhibeerders, vankomisien, kotrimoksasool, NSAID's, gansiklovir of asiklovir). Verbeterde nefrotoksisiteit is waargeneem na toediening van amfoterisien B en ibuprofeen saam met takrolimus. Immuunonderdrukkers kan die reaksie op inenting beïnvloed en inenting tydens takrolimusbehandeling kan minder effektief wees. Die gebruik van lewende verswakte entstowwe moet vermy word (sien afdeling 4.3).

4.6 Vrugbaarheid, swangerskap en laktasie
Swangerskap
TALOMUNE is teenaangedui tydens swangerskap. In diere studies (rotte en konyne), is dit aangetoon dat takrolimus teratogenies is teen dosisse wat ook vir die moeder toksies was. Prekliniese en menslike data toon dat takrolimus die plasenta kan kruis. Die moontlikheid van swangerskap moet dus uitgesluit word voordat TALOMUNE behandeling begin word.
Borsvoeding
Prekliniese data in rotte dui daarop dat takrolimus in borsmelk uitgeskei word. Menslike data op die effekte van takrolimus tydens laktasie is beperk. Aangesien skadelike effekte op die pasgeborene nie uitgesluit kan word nie, moet vrouens nie borsvoed terwyl hulle TALOMUNE ontvang nie.
Vrugbaarheid
'n Negatiewe effek van TALOMUNE op manlike vrugbaarheid in die vorm van verminderde spermtellings en beweeglikheid is by rotte waargeneem.

4.7 Effekte op die vermoë om te bestuur en gebruik van masjiene
TALOMUNE word met visuele en neurologiese versteurings geassosieer. Pasiente wat met TALOMUNE behandel word en deur sulke afwykings geaffekteer word, moenie 'n motor bestuur of gevaarlike masjinerie hanteer nie. Hierdie effek kan versterk word indien TALOMUNE saam met alkohol gebruik word.

4.8 Ongewenste effekte
a. Opsomming van die veiligheidsprofiel
Die profiel van die newe-effekte wat verband hou met immuunonderdrukkende medisyne, is dikwels moeilik om vas te stel vanweë die onderliggende siekte en die gelyktydige gebruik van veelvuldige medisyne. Daar is bewyse dat sommige van die onderstaande gebeure omkeerbaar is en op dosisverlaging reageer. Dit lyk of orale toediening verband hou met 'n laer voorkoms van newe-effekte in vergelyking met intraveneuse gebruik.

b. Getabelleerde opsomming van nadelige reaksies
Die volgende nadelige reaksies is aangemeld tydens kliniese studies en/of gebruik na bemarking:

MedDRA-stelsel orgaanklas	Frekwensie	Nadelige reaksies
Infeksies en infestasies	Dikwels	Verhoogde risiko vir infeksies (viraal, bakterieël, mikobakterieël, fungus, protosoïes). Die verloop van voorafbestaande infeksies kan vererger word. Beide algemene en gelokaliseerde infeksies kan voorkom (sien afdeling 4.4)
	Frekwensie onbekend	Gevalle van progressiewe multifokale leukoensefalopatie (PML), soms noodlottig; -polioma-virus geassosieerde nefropatie (PVAN), insluitend verlies van oorplantingsweefsel (sien afdeling 4.4)
Neoplasmas: benigne, kwaadaardige en ongespesifiseerde (insl. siste and poliepe)	Minder dikwels	Verhoogde risiko om kwaadaardighede te ontwikkel. Benigne asook maligne neoplasmas, insluitende Epstein-Barr Virus (EBV)-geassosieerde limfoproliferatiewe afwykings en vel kwaadaardighede (sien afdeling 4.4) is aangemeld.
Bloed en limfatiese sisteem afwykings	Dikwels	Anemie, leukopenie, trombositopenie, leukositose, rooibloedsel analise abnormaal.
	Minder dikwels	Koagulopatie, koagulasie en bloedingsanalise abnormaal, pansitopenie, trombotiese trombositopeniese purpura, hipoprotrombinemie (sien afdeling 4.4).
	Frekwensie onbekend	Agranulositose, verspreide intravaskulêre stolling, hemolitiese anemie, suiwer rooisel aplasie (sien afdeling 4.4)
Immuun stelsel afwykings	Minder dikwels	Allergiese en anafilakotoïede reaksies
Endokrien afwykings	Minder dikwels	Hirsutisme
Metabolisme- en voeding afwykings	Dikwels	Hiperglisemiese toestande, diabetes mellitus, hiperkalemie, hipomagnesemie, hipofosfatemie, hipokalemie, hipokalsemie, hiponatremie, vloeistofoorlading, hiperurisemie, verlaagde eetlus, anoreksie, metaboliese asidose, hiperlipidemie, hipercholesterolemie, hipertrigliseridemie, ander elektroliet abnormaliteite
	Minder dikwels	Dehidrasie, hipoproteïnemie, hiperfosfatemie, hipoglisemie
	Frekwensie onbekend	Glikosurie, verhoogde amilase insluitend pankreatitis, gewigsverlies
Psigiatriese afwykings	Dikwels	Slapeloosheid, angs simptome, verwarring en disoriëntasie, depressie, veranderings in gemoed, nagmerries, hallusinasie, geestesversteuring
	Minder dikwels	Psigotiese versteuring
Senustelselafwykings	Dikwels	Bewing, hoofpyn, stuipe, versteurings in bewustheid, parestesie en disestesie, periferiese neuropatie, duiseligheid, belemmering om te skryf, senustelsel afwykings
	Minder dikwels	Koma, sentrale senustelsel bloedings en serebrovaskulêre toevalle, paralise en parese, ensefalopatie, spraak- en taal abnormaliteite, amnesie, hipertonie, miastenie
	Frekwensie onbekend	Karpale tonnelsindroom, serebrale infarksie, hemiparese, leuko-enkefalopatie, geestesversteuring, mutisme, agterste omkeerbare enkefalopatiesindroom (PRES) (sien afdeling 4.4), progressiewe multifokale leuko-enkefalopatie (PML) (sien afdeling 4.4), kwadriplegie, sinkopee
Oog afwykings	Dikwels	Dowwe visie, fotofobie, oog afwykings
	Minder dikwels	Katarak
Oor- en labirint afwykings	Dikwels	Tinnitus
	Minder dikwels	Hipo-akuse, neuro-sensoriese doofheid, belemmerde gehoor
Kardiale afwykings	Dikwels	Iskemiese koronêre arterie afwykings, tagikardie
	Minder dikwels	Ventrikulêre disritmie en hartstilstand, hartversaking, kardiomiopatie, ventrikulêre hipertrofie, supraventrikulêre disritmie, palpitasies, EKG ondersoeke abnormaal, harttempo en pols ondersoeke abnormaal, perikardiale effusie, eggokardiogram abnormaal
	Frekwensie onbekend	Atriale fibrillasie, atriale fladder, abnormale T-golf van die elektrokardiogram, gloede, perikardiale effusie, QT-verlenging, Torsade de Pointes, ventrikulêre ekstrasistole, ventrikulêre fibrillasie (sien afdeling 4.4)
Vaskulêre afwykings	Dikwels	Hipertensie, bloeding, trombo-emboliese en iskemiese gebeurtenisse, perifere vaskulêre afwykings, vaskulêre hipotensiewe versteurings
	Minder dikwels	Miokardiale infarksie, diep veneuse trombose skok, miokardiale iskemie, miokardiale hipertrofie
Respiratoriese-, torakale- en medistinale afwykings	Dikwels	Dispnee, parengimatiese long afwykings, pleurale effusie, faringitis, hoes, nasale kongestie en inflammasie
	Minder dikwels	Respiratoriese versakings, akute respiratoriese nood sindroom, respiratoriese kanaal afwykings, asma
	Frekwensie onbekend	Interstisiële longsiekte, longinfiltrasie
Gastro-intestinale afwykings	Dikwels	Diarree, naarheid, gastro-intestinale inflammatoriese toestande, gastro-intestinale ulserasie en perforasie, gastro-intestinale bloedings, askites, braking, gastro-intestinale en abdominale pyne, dispeptiese tekens en simptome, hardlywigheid, winderigheid, buikswelling en distensie, los stoelgang, gastro-intestinale tekens en simptome, stomatitis en ulserasie
	Minder dikwels	Paralitiese ileus, peritonitis, akute en chroniese pankreatitis, verhoogde bloed amilase, gastro-esofageale refluks siekte, belemmerde maag lediging, subileus, pankreatiese pseudosist
	Frekwensie onbekend	Kolitis, enterokolitis, gastro-enteritis, hemorragiese pankreatitis, nekrotiseerde pankreatitis
Hepatobiliêre afwykings	Dikwels	Hepatiese ensieme en funksie abnormaliteite, cholestase en geelsug, hepatosellulêre skade en hepatitis, cholangitis
	Minder dikwels	Hepatiese arterie trombose, veno-okklusiewe lewersiekte, hepatiese versaking, galbuis stenose
	Frekwensie onbekend	Hepatiese sitolise, hepatiese nekrose, hepatotoksisiteit, vetterige lewer
Vel en subkutane weefsel afwykings	Dikwels	Pruritus, uitslag, alopesie, aknee, vermeerderde sweet
	Minder dikwels	Dermatitis, fotosensitiwiteit, toksiese epidermale nekrolise (Lyell se sindroom), Stevens-Johnson sindroom
Muskuloskeletale- en bindweefsel afwykings	Dikwels	Artralgie, spierkrampe, pyn in ledemate, rugpyn
	Minder dikwels	Gewrig afwykings
	Frekwensie onbekend	Pyn in die uiterste ledemate, insluitend Kalsineurien-Remmer-Geïnduseerde Pyn Sindroom (CIPS).
Renale- en urinêre afwykings	Dikwels	Akute nierversaking, nierbeskadiging, nierversaking, oligurie, nierbuis nekrose, toksiese nefropatie, urinere abnormaliteite, blaas en uretra simptome
	Minder dikwels	Hemolitiese uremiese sindroom, hemorragiese sistitis, nefropatie, anurie
Voorplantingstelsel en bors afwykings	Minder dikwels	Dismenorree en baarmoederbloeding
Algemene afwykings en toestande by plek van toediening	Dikwels	Versteurde liggaamstemperatuur persepsie, asteniese toestande, koorsversteurings, edeem, pyn en ongemak, verhoogde bloed alkaliese fosfatase, gewigstoename
	Minder dikwels	Senuweeagtige gevoel, multi-orgaanversaking, griepagtige siekte, temperatuur onverdraagsaamheid, drukking op borskas, abnormale gevoel, verhoogde bloedlaktaat dehidrogenase, gewigsafname, dors, val, benoudheid in bors, afname in beweeglikheid, ulkus, toename in vetweefsel
	Frekwensie onbekend	Warm gloede
Ondersoeke	Frekwensie onbekend	Gereelde monitering van die volgende parameters moet op 'n roetine basis onderneem word: bloeddruk, EKG, neurologiese en visuele status, vastende bloedglukose vlakke, elektroliete (veral kalium), lewer- en renale funksie toetse, hematologiese parameters, koagulasie waardes en plasmaproteïen bepalings.
Besering, vergiftiging en prosedure komplikasies	Dikwels	Primêre weefseloorplanting disfunksie, foute met gebruik van medisyne, insluitend onbewuste, onopsetlike, of ongekontroleerde substitusie van onmiddellike- of verlengde-vrystelling takrolimus formulerings, is waargeneem (sien afdeling 4.4)
	Frekwensie onbekend	'n Aantal geassosieerde gevalle van oorplanting verwerping is gerapporteer

Aanmelding van vermoedelike nadelige reaksies
Dit is belangrik om newe-effekte wat vermoed word na die medisyne gemagtig is, te rapporteer. Dit laat die voortgesette monitering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsverskaffers word gevra om enige vermoedens van newe-effekte aan te meld by SAHPRA deur die "**6.04 Adverse Drug Reaction Reporting Form**", wat aanlyn gevind word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering
Ondervinding met oordosering is beperk.
Vroeë kliniese ondervinding (toe aanvanklike induksiedosisse 2 of 3 keer groter was as die wat tans aanbeveel word) het aangetoon dat simptome van oordosering renale, neurologiese en kardiale versteurings, glukose intoleransie, hipertensie en elektroliet afwykings (bv. hiperkalemie) kan insluit. Oor-immuunonderdrukking kan die risiko vir ernstige infeksies verhoog. Lewerfunksie beïnvloed duidelik alle pre- en post-operatiewe farmakokinetiese veranderlikes. Pasiente met lewer-weefseloorplantings wat verswak of die wat van ander immuunonderdrukkende behandeling na TALOMUNE oorgeskakel word, moet versigtig gemonitor word om oordosering te voorkom. Geen spesifieke teenmiddel vir TALOMUNE is beskikbaar nie. Indien oordosering voorkom, moet algemene ondersteunende maatreëls en simptomatiese behandeling ingestel word. Gebaseer op die swak wateroplosbaarheid en ekstensiewe binding aan eritrosiete en plasmaproteïene word dit verwag dat TALOMUNE nie dialiseerbaar sal wees nie. In geïsoleerde pasiënte met baie hoe takrolimus plasmakonsentrasies was dit gerapporteer dat hemofiltrasie en hemodiafiltrasie die takrolimusvlakke beduidend verminder het. In gevalle van orale oordosering kan maagspoeling en/of die gebruik van absorbeermiddels (soos geaktiveerde houtskool) nuttig wees.

5 FARMAKOLOGIESE EIENDOMME
5.1 Farmakodinamiese eienskappe
Farmakoterapeutiese groep: Kalsineurien-inhibeerders ATC Kode: L04AD02
Meganisme van aksie
Takrolimus is 'n immuunonderdrukkende middel met aktiwiteit in beide *in vitro* en *in vivo* eksperimente. In besonder, inhibeer takrolimus die vorming van sitotoksiese limfosiete, wat hoofsaaklik verantwoordelik is vir oorplantingsverwerping. Takrolimus onderdruk T-sel aktivering en T-hulpsel afhanklike B-sel proliferasie, asook die vorming van limfokiene soos interleukiene-2, -3, en y-interferon en die ekspressie van die interleukien-2 reseptor. Op molekulêre vlak blyk dit dat takrolimus se effekte deur binding aan 'n sitosoïese proteïen (FKBP) bemiddel word, wat ook verantwoordelik is vir die intrasellulêre akkumulasie van die verbinding.

5.2 Farmakokinetiese eienskappe
Algemene eienskappe
Absorpsie
In die rot is die boonste gastroïntestinale weg as die belangrikste plek van absorpsie geïdentifiseer.
Die absorpsie van takrolimus is onvolledig en uiters wisselend na orale toediening. Na orale toediening word takrolimus in sommige pasiënte vinnig geabsorbeer met piek plasmakonsentrasies wat binne 0,5 tot 3 uur bereik word, terwyl dit voorkom asof dit in ander pasiënte deurlopend oor 'n lang periode geabsorbeer word wat 'n relatiewe plat absorpsieprofiel lewer. Swak dissolusie van takrolimus in gastriese vloeistowwe vanweë lae wateroplosbaarheid en veranderinge in gastriese beweeglikheid kan gedeeltelik vir hierdie waarneming verantwoordelik wees. In nier-alloweefseloorplanting pasiënte het enkele orale dosisse van 0,10; 0,15 en 0,2 mg/kg piek bloedkonsentrasies van 19,2; 24,2 en 47,9 ng/ml, respektiewelik gelewer. Die tyd tot piek konsentrasie het van 0,7 tot 6 uur gewissel. Die gemiddelde biobeskikbaarheid van takrolimus kapsules is beraam as 21,8 % in leweroorplantingspasiënte, 20, 1 % in nieroorplantingspasiënte, 14,4 tot 17,4 % in gesonde persone en 25 % in pediatriese leweroorplantingspasiënte. In ontvangers van hart-alloweefseloorplanting word takrolimus geabsorbeer met 'n gemiddelde tyd tot piek konsentrasie (t_{maks}) van ongeveer 1,5 uur. Die orale biobeskikbaarheid van takrolimus is gemiddeld 20 %, alhoewel daar 'n hoe mate van pasiënt wisselvalligheid in hartoorplantingspasiënte is. Die orale biobeskikbaarheid van takrolimus was verminder indien dit na 'n maaltyd met matige vetinhoud toegedien is. Daar was 'n afname in AOK (plasma 27 %, heelbloed 35 %), C_{maks} (plasma 50 %, heelbloed 57 %), en 'n toename in t_{maks} (beide plasma en heelbloed 173 %). Beide die tempo en die mate van absorpsie was verlaag indien takrolimus saam met voedsel gegee is. Gal beïnvloed nie die absorpsie van takrolimus nie, daarom is aanvang van takrolimus behandeling met 'n orale dosis en vroeë oorskakeling van leweroorplantingspasiënte na orale behandeling moontlik.
Verspreiding en uitskeiding
Verspreiding van takrolimus is ekstensief. Dit bind tot 'n hoe mate aan rooibloedselle en aan plasmaproteïene. Na intraveneuse infusie van takrolimus word piek plasmakonsentrasies aan die einde van die infusie bereik. Konsentrasie neem vinnig af na die einde van die infusie wat 'n vinnige verspreiding van die middel buite die plasmakompartement aandui. Sodra verspreidingsewewig bereik is, neem takrolimuskonsentrasies teen 'n stadiger tempo af wat ooreenstem met die eienskappe van die medisyne. Die farmakokinetika van takrolimus na intraveneuse infusie by oorplantingspasiënte kan deur 'n twee kompartement-model beskryf word. In nieroorplantingspasiënte was die toename in AOK en C_{maks} na 'n enkele orale dosis post-oorplanting proporsioneel tot die toename in orale dosis. In leweroorplantingspasiënte het die gemiddelde trogvlakkonsentrasies van takrolimus vir tot 6 maande post-oorplanting betreklik stabiel gebly. Gebaseer op data van plasmavlakke in oorplantingspasïente, is die volume van verspreiding gemiddeld 1342 l wat dui op ekstensiewe verspreiding van takrolimus in die liggaam. In leweroorplantingspasiënte is die volume van verspreiding gemiddeld 64,4 l gebaseer op heelbloedkonsentrasies (0,85 l/kg wanneer genormaliseer teenoor liggaamsmassa). Meting van minimumvlakke in bloed of plasma, wat met die AOK gekorreleer is, het 'n akkurate weerspieëling van totale takrolimus blootstelling verskaf. Takrolimus het hoë binding aan plasmaproteïene (> 98,8 %) in rotte, honde, ape en die mens. Dit blyk dat die heelbloed/plasmaverhouding ongeveer 20:1 is (studies met vrywilligers). Takrolimus bind sterk aan eritrosiete. Hierdie effek is afhanklik van temperatuur, laer temperature het laer plasmakonsentrasies tot gevolg. Na orale toediening (0,15 mg/kg twee maal daagliks) aan leweroorplantingspasiënte is ewewigstoestand konsentrasies van takrolimus in die meeste pasiënte binne 3 dae bereik. Die halfleeftyd van takrolimus is lank en wisselend, en opruiming laag. Die gemiddelde totale liggaamsopruiming is ongeveer 30 ml/min/g (7 - 103 ml/min/kg). In leweroorplantingspasiënte is die totale liggaamsopruiming waargeneem as 4,5 l/h (heelbloedkonsentrasies) en 150,1 l/h of 2,0 l/h/kg wanneer teenoor liggaamsmassa genormaliseer (plasmakonsentrasies). Die plasma halfleeftyd van takrolimus wissel tussen 3,5 and 40,5 h in nieroorplantingspasiënte, ander bronne vermeld tot 50 h. In leweroorplantingspasïente is die eliminasie halfleeftyd gebaseer op die heelbloedkonsentrasie gemiddeld 11,7 h (reikwydte 6,1 - 20,9 h) en gebaseer op plasmakonsentrasies 6,5 h (reikwydte 2,7 - 13,3 h). Die renale opruiming is minder as 1 ml/min. Die metaboliete van takrolimus word hoofsaaklik deur die gal uitgeskei. Die gemiddelde orale opruiming en volume van verspreiding was gemiddeld 0,21 ± 0,08 l/h/kg en 2,4 ± 0,8 l/kg terwyl $t_{1/2}$ gemiddeld 8,7 ± 3,5 ure in hartoorplantingspasiënte was.
Metabolisme en biotransformasie
Takrolimus word tot 'n groot mate in die lewer gemetaboliseer, hoofsaaklik deur die sitochroom P450-3A4 familie. Takrolimus word ook beduidend in die intestinale wand gemetaboliseer. Daar is verskeie metaboliete geïdentifiseer. Slegs een hiervan het *in vitro* immuunonderdrukkende aktiwiteit soortgelyk aan die van takrolimus getoon. Die ander metaboliete het slegs swak of geen immuunonderdrukkende aktiwiteit nie. In sistemiese sirkulasie is slegs een van die onaktiewe metaboliete teen lae konsentrasies teenwoordig. Gevolglik dra metaboliete nie by tot die farmakologiese aktiwiteit van takrolimus nie.
Uitskeiding
Na intraveneuse en mondelikse toediening van ^{14}C-gemerkte takrolimus, was meeste van die radio-aktiwiteit in die ontlasting uitgeskei. Ongeveer 2 % van die radio-aktiwiteit was in die uriene uitgeskei. Minder as 1 % van onveranderde takrolimus is in die uriene en ontlasting bespeur, wat daarop dui dat takrolimus byna heeltemal gemetaboliseer word voor uitskeiding: gal is die hoofroete van uitskeiding.
Eienskappe in pasiënte
Verwantskap tussen plasma/bloedkonsentrasies en terapeutiese aktiwiteit
Individuele dosisaanpassing wat beheer word deur monitering van takrolimusvlakke in heelbloed kan nuttig wees om optimale terapie te bereik. Verskeie immuunanalises is beskikbaar vir die bepaling van takrolimuskonsentrasies in heelbloed, insluitende 'n volle outomatiese mikrodeeltjie ensiem-immuunanalise (MEIA).
Variasies ten opsigte van beperkende faktore, ouderdom, polimorfisme, metabolisme en gepaardgaande patologiese toestande (nierversaking, hepatiese ontoereikendheid)
Gebaseer op voorlopige kliniese ondervinding word die kinetiese eienskappe van takrolimus nie in bejaarde pasiënte verander nie. Kinders benodig 'n hoër dosis van takrolimus; ongeveer 1½ - 2 keer hoër as wat vir volwassenes aanbeveel word, moontlik vanweë 'n hoër metaboliese omset.
Pasiënte met lewerdisfunksie
Pasiënte met lewerdisfunksie het geneig om hoër takrolimuskonsentrasies (en ooreenstemmende langer halfleeftye en kleiner opruimingswaardes) in vergelyking met pasiënte met normale lewerfunksie te hê. Aangesien takrolimus ekstensief deur die lewer gemetaboliseer word, moet pasiënte met verswakte lewerfunksie sorgvuldig gemonitor word en 'n dosisaanpassing kan nodig wees.
Pasiënte met nierdisfunksie
Aangesien takrolimus bykans volledig gemetaboliseer word, hoogs lipiedoplosbaar is, en 'n molekulêre massa van 822 g/mol het, word dit nie verwag dat dit dialiseerbaar sal wees nie. Daarby word minder as 1 % van 'n toegediende intraveneuse dosis in die uriene uitgeskei. Daarom is aanpassings in die dosisregimen uit 'n farmakokinetiese oogpunt nie nodig in pasiënte met nierversaking of in pasiënte wat dialise ondergaan nie. Dosisaanpassing kan egter nodig wees in pasiënte met tekens van medisyne geïnduseerde verswakking van nierfunksie.

5.3 Prekliniese veiligheidsdata
Karsinogenese
Karsinogeniese-studies by manlike en vroulike rotte en muise het getoon dat daar geen verband tussen die voorkoms van gewas en die dosis van takrolimus is nie. (sien Geboksde Waarskuwingen afdeling 4.4).
Mutagenese
Geen bewyse van genotoksisiteit is gesien in bakteriële (*Salmonella* en *E. coli*) of soogdier (Chinese hamster long-afgeleide selle) *in vitro*-toetse vir mutageniteit, die *in vitro* CHO/HGPRT-toets vir mutagenisiteit, of *in vivo*-klastogenisiteit-toetse wat by muise uitgevoer is nie; takrolimus het nie onbeplande DNA-sintese in knaagdiere-hepatosiete veroorsaak nie.
Inkorting van vrugbaarheid
Takrolimus wat mondeliks toegedien word aan manlike en vroulike rotte, voor en tydens paring, sowel as aan damme tydens dragtigheid en laktasie, hou verband met embrio-letaliteit en nadelige effekte op vroulike voortplanting. Effekte op vroulike voortplantingsfunksie (bevalling) en embrio-dodelike effekte is aangedui deur 'n hoër tempo van verlies aan voor- en na-inplanting en 'n toename in aantal nie-lewende en nie-lewensvatbare kleintjies. Wanneer 2,6 tot 6,9 keer die kliniese dosisreeks toegedien is, gebaseer op liggaamsoppervlakte, is takrolimus geassosieer met toksisiteit van moeder en vader, sowel as reproduktiewe toksisiteit, insluitend duidelike nadelige effekte op estrussiklusse, bevalling, lewensvatbaarheid by kleintjies en misvormings van kleintjies.

6 FARMASEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Kapsule inhoud: Kroskarmellose natrium, Hipromellose 2910, Laktosemonohidraat, Magnesiumstearaat (E572).
Kapsuledop:
Die 0,5 mg kapsuledop bevat, FD & C Blou 1 (E133), FD & C Rooi 40 (E129), gelatien en titaandioksied (E171).
Die 1 mg kapsuledop bevat FD & C Blou 1 (E133), gelatien, ysteroksied geel (E172) en titaandioksied (E171).
Die 5 mg kapsuledop bevat D & C Rooi 28, D & C Geel 10 (E104), FD & C Blou 1, gelatien, en titaandioksied (E171).

6.2 Onverenigbaarhede
Nie van toepassing.

6.3 Raklewe
36 maande.

6.4 Spesiale voorsorgmaatreëls vir berging
Bere by of onder 25 °C. Hou in die oorspronklike verpakking totdat dit benodig word.
HDPE Bottels: Hou die bottel styf toe.
Stulpstroke: Moenie die stulpstroke van die karton verwyder totdat dit benodig word vir gebruik nie.

6.5 Aard en inhoud van die houer
HDPE houer: 30 of 100 kapsules verpak in 'n deursigtige, ronde 50 ml HDPE houer, toegemaak met 'n wit, ondeursigtige plastiek dop.
Stulpverpakking: 10 kapsules verpak in aluminium folie (PVC/PVDC) stulpstroke. 10 sulke stulpstroke sal verpak word binne 'n gedrukte karton.
Verpakkingsgrootte: 100 kapsules.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering
Geen spesiale vereistes nie.

7 HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE
Strides Pharma SA (Edms) Bpk
16de Weg 106, Gebou 2, Midrand, Suid Afrika, 1686

8 REGISTRASIE NOMMERS
TALOMUNE 0,5 mg 54/32.16/0811; 1 mg 54/32.16/0812; 5 mg 54/32.16/0813

9 DATUM VAN EERSTE MAGTIGING/HERNUWING VAN DIE MAGTIGING
Die datum op die registrasie sertifikaat van die medisyne.

10 DATUM VAN HERSIENING VAN DIE TEKS