Siromune®

Sirolimus

FORMS AND PRESENTATION
Siromune®: Film coated tablets: Box of 100.
COMPOSITION
Siromune®: Each film coated tablet contains Sirolimus 1mg.
Excipients: starch, lactose, povidone, talc, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Therapeutic class: Immunosuppressants.
ATC code: L04AA10.
Sirolimus inhibits T-cell activation induced by most stimuli, by blocking calcium-dependent and calcium-independent intracellular signal transduction. Studies demonstrated that its effects are mediated by a mechanism that is different from that of cyclosporine, tacrolimus, and other immunosuppressive agents. Experimental evidence suggests that Sirolimus binds to the specific cytosolic protein FKPB-12, and that the FKPB 12-Sirolimus complex inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a critical kinase for cell cycle progression. The inhibition of mTOR results in blockage of several specific signal transduction pathways. The net result is the inhibition of lymphocyte activation, which results in immunosuppression.
In animals, Sirolimus has a direct effect on T- and B-cell activation, suppressing immune-mediated reactions, such as allograft rejection.
Pharmacokinetic properties
Absorption
In 24 healthy volunteers receiving Sirolimus tablets with a high-fat meal, C_{max}, t_{max} and AUC showed increases of 65%, 32%, and 23%, respectively. To minimize variability, Sirolimus tablets should be taken consistently with or without food. Grapefruit juice affects CYP3A4-mediated metabolism and must, therefore, be avoided.
Distribution
The mean (± SD) blood-to-plasma ratio of Sirolimus was 36 ± 18 in stable renal allograft patients, indicating that Sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (Vss/F) of Sirolimus is 12 ± 8 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins, mainly serum albumin (97%), α1-acid glycoprotein, and lipoproteins.
Biotransformation
Sirolimus is a substrate for both CYP3A4 and P-gp. Sirolimus is extensively metabolized in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen. Inhibitors of CYP3A4 and P-gp increase Sirolimus concentrations. Inducers of CYP3A4 and P-gp decrease Sirolimus concentrations. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.
Elimination
The mean ± SD terminal elimination half life (t½) of Sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.
INDICATIONS
Siromune® is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended that Siromune® be used initially in combination with cyclosporine micro-emulsion and corticosteroids for 2 to 3 months. Siromune® may be continued as maintenance therapy with corticosteroids only if cyclosporine micro-emulsion can be progressively discontinued.
CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
PRECAUTIONS
Sirolimus has not been adequately studied in patients at high immunological risk, therefore use is not recommended in this group of patients.
In patients with delayed graft function, Sirolimus may delay recovery of renal function.
- Hypersensitivity reactions: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis, have been associated with the administration of Sirolimus.
- Immunosuppressive agents: Sirolimus has been administered concurrently with the following agents in clinical studies: Tacrolimus, cyclosporine, azathioprine, mycophenolate mofetil, corticosteroids and cytotoxic antibodies. Sirolimus in combination with other immunosuppressive agents has not been extensively investigated.
Renal function should be monitored during concomitant administration of Sirolimus and cyclosporine. Appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels. Caution should be exercised when co-administering other agents that are known to have a deleterious effect on renal function.
Patients treated with cyclosporine and Sirolimus beyond 3 months had higher serum creatinine levels and lower calculated glomerular filtration rates compared to patients treated with cyclosporine and placebo or azathioprine controls. Patients who were successfully withdrawn from cyclosporine had lower serum creatinine levels and higher calculated glomerular filtration rates, as well as lower incidence of malignancy, compared to patients remaining on cyclosporine. The continued co-administration of cyclosporine and Sirolimus as maintenance therapy cannot be recommended.
Based on information from subsequent clinical studies, the use of Sirolimus, mycophenolate mofetil, and corticosteroids, in combination with IL-2 receptor antibody (IL2R Ab) induction, is not recommended in the de novo renal transplant setting.
Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors to Sirolimus in maintenance renal transplant patients, increased urinary protein excretion was commonly observed at 6 to 24 months after conversion to Sirolimus. New onset nephrosis (nephrotic syndrome) was also reported in 2% of the patients in the study. The safety and efficacy of conversion from calcineurin inhibitors to Sirolimus in maintenance renal transplant patients have not been established. The concomitant use of Sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA).
- HMG-CoA reductase inhibitors: In clinical studies, the concomitant administration of Sirolimus and HMG-CoA reductase inhibitors and/or fibrates was well-tolerated. During Sirolimus therapy with or without CsA, patients should be monitored for elevated lipids, and patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse reactions.
- Cytochrome P450 isozymes: Co-administration of Sirolimus with strong inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampin, rifabutin) is not recommended.
- Angiotensin-converting enzyme inhibitors (ACE): The concomitant administration of Sirolimus and angiotensin-converting enzyme inhibitors has resulted in angioneurotic edema-type reactions.
- Vaccination: Immunosuppressants may affect response to vaccination. During treatment with immunosuppressants, including Sirolimus, vaccination may be less effective. The use of live vaccines should be avoided during treatment with Sirolimus.
- Malignancy: Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression. As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
- Infections: Over-suppression of the immune system can also increase susceptibility to infection, including opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections, and sepsis.
Among these conditions are BK virus-associated nephropathy and JC virus-associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.
Cases of Pneumocystis carinii pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for Pneumocystis carinii pneumonia should be administered for the first 12 months following transplantation.
Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.
- Hepatic impairment: In hepatically impaired patients, it is recommended that Sirolimus whole blood trough levels be closely monitored. In patients with severe hepatic impairment, reduction in maintenance dose by one half is recommended based on decreased clearance. Since half-life is prolonged in these patients, therapeutic monitoring of the medicinal product after a loading dose or a change of dose should be performed for a prolonged period of time until stable concentrations are reached.
- Lung and liver transplant populations: The safety and efficacy of Sirolimus as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore such use is not recommended.
- Systemic effects: There have been reports of impaired or delayed wound healing in patients receiving Sirolimus, including lymphocele and wound dehiscence. Patients with a body mass index (BMI) greater than 30 kg/m² may be at increased risk of abnormal wound healing based on data from the medical literature.
There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion and pericardial effusions (including hemodynamically significant effusions in children and adults), in patients receiving Sirolimus.
The use of Sirolimus in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment. Patients administered Sirolimus should be monitored for hyperlipidemia using laboratory tests and if hyperlipidemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents should be initiated. The risk/benefit should be considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen, including Sirolimus. Similarly the risk/benefit of continued Sirolimus therapy should be re-evaluated in patients with severe refractory hyperlipidemia.
- Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
PREGNANCY AND LACTATION
Effective contraception must be used during Sirolimus therapy and for 12 weeks after Sirolimus has been stopped.
There are no adequate data from the use of Sirolimus in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Sirolimus should not be used during pregnancy unless clearly necessary. Effective contraception must be used during Sirolimus therapy and for 12 weeks after Sirolimus has been stopped.
Following administration of radio-labeled Sirolimus, radioactivity is excreted in the milk of lactating rats. It is not known whether Sirolimus is excreted in human milk. Because of the potential for adverse reactions in breast-fed infants from Sirolimus, breast-feeding should be discontinued during therapy.
Impairments of sperm parameters have been observed among some patients treated with Sirolimus. These effects have been reversible upon discontinuation of Sirolimus in most cases.
DRUG INTERACTIONS
Sirolimus is extensively metabolized by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp) located in the small intestine. Therefore, absorption and the subsequent elimination of Sirolimus may be influenced by substances that affect these proteins. Inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) decrease the metabolism of Sirolimus and increase Sirolimus levels. Inducers of CYP3A4 (such as rifampin or rifabutin) increase the metabolism of Sirolimus and decrease Sirolimus levels. Co-administration of Sirolimus with strong inhibitors of CYP3A4 or inducers of CYP3A4 is not recommended.
- Rifampicin (CYP3A4 inducer): Rifampicin is a strong inducer of CYP3A4 and P-gp; co-administration of Sirolimus tablets and rifampicin is not recommended. In patients where rifampicin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.
- Ketoconazole (CYP3A4 inhibitor): Ketoconazole is a strong inhibitor of CYP3A4 and P-gp; co-administration of Sirolimus tablets and ketoconazole is not recommended.
- Voriconazole (CYP3A4 inhibitor): Co-administration of Sirolimus (2 mg single dose) with multiple-dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 100 mg every 12 hours for 8 days) in healthy subjects has been reported to increase Sirolimus C_{max} and AUC by an average of 7-fold and 11-fold, respectively. Co-administration of Sirolimus and voriconazole is not recommended.
- Diltiazem (CYP3A4 inhibitor): Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp. If diltiazem is administered, Sirolimus blood levels should be monitored and a dose adjustment may be necessary.
- Verapamil (CYP3A4 inhibitor): Verapamil is a substrate and inhibitor of CYP3A4 and P-gp. Sirolimus levels should be monitored, and appropriate dose reductions of both medicinal products should be considered.
- Erythromycin (CYP3A4 inhibitor): Erythromycin is a substrate and inhibitor of CYP3A4 and P-gp. Sirolimus levels should be monitored and appropriate dose reductions of both medicinal products should be considered.
- Cyclosporine (CYP3A4 substrate): The rate and extent of Sirolimus absorption was significantly increased by cyclosporine A (CsA). Sirolimus administered concomitantly (5 mg), and at 2 hours (5 mg) and 4 hours (10 mg) after CsA (300 mg), resulted in increased Sirolimus AUC by approximately 183%, 141% and 80%, respectively. The effect of CsA was also reflected by increases in Sirolimus C_{max} and t_{max}. When given 2 hours before CsA administration, Sirolimus C_{max} and AUC were not affected. Single-dose Sirolimus did not affect the pharmacokinetics of cyclosporine (micro-emulsion) in healthy volunteers when administered simultaneously or 4 hours apart. It is recommended that Sirolimus be administered 4 hours after cyclosporine (micro-emulsion).
- Oral contraceptives: Although the results of a single-dose interaction study with an oral contraceptive suggest the lack of a pharmacokinetic interaction, the results cannot exclude the possibility of changes in the pharmacokinetics that might affect the efficacy of the oral contraceptive during long-term treatment with Sirolimus.
- Other possible interactions: Moderate and weak inhibitors of CYP3A4 may decrease the metabolism of Sirolimus and increase Sirolimus blood levels (e.g., calcium channel blockers: Nicardipine; antifungal agents: Clotrimazole, fluconazole; antibiotics: Troleandomycin; other substances: Bromocriptine, cimetidine, danazol, protease inhibitors).
Inducers of CYP3A4 may increase the metabolism of Sirolimus and decrease Sirolimus blood levels (e.g., St. John's Wort (Hypericum perforatum), anticonvulsants: Carbamazepine, phenobarbital, phenytoin).
Although Sirolimus inhibits human liver microsomal cytochrome P_{450} CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 in vitro, the active substance is not expected to inhibit the activity of these isozymes in vivo since the Sirolimus concentrations necessary to produce inhibition are much higher than those observed in patients receiving therapeutic doses of Sirolimus. Inhibitors of P-gp may decrease the efflux of Sirolimus from intestinal cells and increase Sirolimus levels.
Grapefruit juice affects CYP3A4-mediated metabolism, and should therefore be avoided.
Pharmacokinetic interactions may be observed with gastrointestinal prokinetic agents, such as cisapride and metoclopramide.
No clinically significant pharmacokinetic interaction was observed between Sirolimus and any of the following substances: Acyclovir, atorvastatin, digoxin, glibenclamide, methylprednisolone, nifedipine, prednisolone, and trimethoprim/sulfamethoxazole.
ADVERSE EFFECTS
The most commonly reported adverse reactions (occurring in >10% of patients) are thrombocytopenia, anemia, pyrexia, hypertension, hypokalemia, hypophosphatemia, urinary tract infection, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, abdominal pain, lymphocele, peripheral edema, arthralgia, acne, diarrhea, pain, constipation, nausea, headache, increased blood creatinine, and increased blood lactate dehydrogenase (LDH).
The incidence of any adverse reaction(s) may increase as the trough Sirolimus level increases.
Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Most patients were on immunosuppressive regimens, which included Sirolimus in combination with other immunosuppressive agents.
- Infections and infestations: Urinary tract infection (very common); sepsis, pneumonia, pyelonephritis, Herpes simplex, fungal, viral, and bacterial infections (such as mycobacterial infections, including tuberculosis, Epstein-Barr virus, CMV, and Herpes zoster) (common); Clostridium difficile, enterocolitis (not known).
- Benign, malignant and unspecified neoplasms (including cysts and polyps): Skin cancer (common); lymphoma/post-transplant lymphoproliferative disorder (uncommon).
- Blood and lymphatic system disorders: Thrombocytopenia, anemia (very common); thrombotic, thrombocytopenic purpura/hemolytic uremic syndrome, leukopenia, neutropenia (common), pancytopenia (uncommon).
- Immune system disorders: Hypersensitivity reactions, including anaphylactic/ anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis (rare).
- Metabolism and nutrition disorders: Hypokalemia, hypophosphatemia, hypercholesterolemia, hyperglycemia, hypertriglyceridemia (very common); diabetes mellitus (common).
- Nervous system disorders: Headache (very common).
- Cardiac disorders: Tachycardia (common); pericardial effusion (including hemodynamically significant effusions in children and adults) (uncommon).
- Vascular disorders: Lymphocele, hypertension (very common); deep vein thrombosis (common); pulmonary embolism (uncommon); lymphedema (rare).
- Respiratory, thoracic, and mediastinal disorders: Pneumonitis, pleural effusion, epistaxis (common); pulmonary hemorrhage (uncommon); alveolar proteinosis (rare).
- Gastrointestinal disorders: Abdominal pain, diarrhea, constipation, nausea (very common); stomatitis, ascites (common); pancreatitis (uncommon).
- Hepatobiliary disorders: Abnormal liver function tests (common), liver failure (not known).
- Skin and subcutaneous tissue disorders: Acne (very common); rash (common).
- Musculoskeletal and connective tissue disorders: Arthralgia (very common); osteonecrosis (common).
- Renal and urinary disorders: Proteinuria (common); nephrotic syndrome (uncommon); focal segmental glomerulosclerosis (not known).
- General disorders and administration site conditions: Peripheral edema, pyrexia, pain (very common); impaired healing, edema (common).
- Investigations: Increased blood lactate dehydrogenase, increased blood creatinine (very common); increased aspartate aminotransferase, increased alanine aminotransferase (common).
- Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin.
- Cases of BK virus-associated nephropathy, as well as cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Sirolimus.
- Hepatoxicity has been reported. The risk may increase as the trough Sirolimus level increases. Rare reports of fatal hepatic necrosis have been reported with elevated trough Sirolimus levels.
- Cases of interstitial lung disease (including pneumonitis and infrequently bronchiolitis obliterans organising pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Sirolimus. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Sirolimus. The risk may be increased as the trough Sirolimus level increases.
- Impaired healing following transplant surgery has been reported, including fascial dehiscence, incisional hernia, and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary).
- Impairments of sperm parameters have been observed among some patients treated with Sirolimus. These effects have been reversible upon discontinuation of Sirolimus in most cases.
- In patients with delayed graft function, Sirolimus may delay recovery of renal function.
- The concomitant use of Sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA.
- Focal segmental glomerulosclerosis has been reported.
- There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion and pericardial effusions (including hemodynamically significant effusions in children and adults) in patients receiving Sirolimus.
- Pediatric population: Controlled clinical studies with posology comparable to that currently indicated for the use of Sirolimus in adults have not been conducted in children or adolescents below 18 years of age. There is insufficient experience to recommend the use of Sirolimus in children and adolescents.
DOSAGE AND ADMINISTRATION
Treatment should be initiated by and remain under the guidance of an appropriately qualified specialist in transplantation.
- Initial therapy (2 to 3 months post-transplantation): The usual dose regimen for Siromune® is a 6 mg single oral loading dose, administered as soon as possible after transplantation, followed by 2 mg once daily until results of therapeutic monitoring of the medicinal product are available. The Siromune® dose should then be individualized to obtain whole blood trough levels of 4 to 12 ng/ml (chromatographic assay). Siromune® therapy should be optimized with a tapering regimen of steroids and cyclosporine micro-emulsion. Suggested cyclosporine trough concentration ranges for the first 2-3 months after transplantation are 150-400 ng/ml (monoclonal assay or equivalent technique).
To minimize variability, Siromune® should be taken at the same time in relation to cyclosporine, 4 hours after the cyclosporine dose, and consistently either with or without food.
- Maintenance therapy: Cyclosporine should be progressively discontinued over 4 to 8 weeks, and the Siromune® dose should be adjusted to obtain whole blood trough levels of 12 to 20 ng/ml. Siromune® should be given with corticosteroids. In patients for whom cyclosporine withdrawal is either unsuccessful or cannot be attempted, the combination of cyclosporine and Siromune® should not be maintained for more than 3 months post-transplantation. In such patients, when clinically appropriate, Siromune® should be discontinued and an alternative immunosuppressive regimen instituted.
Therapeutic monitoring of the medicinal product and dose adjustment: Whole blood Siromune® levels should be closely monitored in the following populations:
- In patients with hepatic impairment;
- When inducers or inhibitors of CYP3A4 are concurrently administered and after their discontinuation and/or if cyclosporine dosing is markedly reduced or discontinued, as these populations are most likely to have special dosing requirements.
Therapeutic monitoring of the medicinal product should not be the sole basis for adjusting Siromune® therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsies, and laboratory parameters.
Most patients who received 2 mg of Siromune® 4 hours after cyclosporine had whole blood trough concentrations of Siromune® within the 4 to 12 ng/ml target range (expressed as chromatographic assay values). Optimal therapy requires therapeutic concentration monitoring of the medicinal product in all patients.
Optimally, adjustments in Siromune® dose should be based on more than a single trough level obtained more than 5 days after a previous dosing change.
Following the discontinuation of cyclosporine therapy, a target trough range of 12 to 20 ng/ml (chromatographic assay) is recommended. Cyclosporine inhibits the metabolism of Siromune®, and consequently Siromune® levels will decrease when cyclosporine is discontinued, unless the Siromune® dose is increased. On average, the Siromune® dose will need to be 4-fold higher to account for both the absence of the pharmacokinetic interaction (2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporine (2-fold increase). The rate at which the dose of Siromune® is increased should correspond to the rate of cyclosporine elimination.
If further dose adjustment(s) are required during maintenance therapy (after discontinuation of cyclosporine), in most patients these adjustments can be based on simple proportion:
New Siromune® dose = current dose x (target concentration/current concentration).
A loading dose should be considered in addition to a new maintenance dose when it is necessary to considerably increase Siromune® trough concentrations:
Siromune® loading dose = 3 x (new maintenance dose - current maintenance dose).
The maximum Siromune® dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading dose should be administered over 2 days. Siromune® trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).
The recommended 24-hour trough concentration ranges for Siromune® are based on chromatographic methods. Several assay methodologies have been used to measure the whole blood concentrations of Siromune®. Currently in clinical practice, Siromune® whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. The concentration values obtained by these different methodologies are not interchangeable. All Siromune® concentrations were either measured using chromatographic methods or have been converted to chromatographic method equivalents. Adjustments to the targeted range should be made according to the assay being utilized to determine the Siromune® trough concentrations. Since results are assay and laboratory dependent, and the results may change over time, adjustment to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. Physicians should therefore remain continuously informed by responsible representatives for their local laboratory on the performance of the locally used method for concentration determination of Siromune®.
Hepatic impairment
The clearance of Siromune® may be reduced in patients with impaired hepatic function. In patients with severe hepatic impairment, it is recommended that the maintenance dose of Siromune® be reduced by approximately one-half.
It is recommended that Siromune® whole blood trough levels be closely monitored in patients with impaired hepatic function. It is not necessary to modify the Siromune® loading dose.
In patients with severe hepatic impairment, monitoring should be performed every 5 to 7 days until 3 consecutive trough levels have shown stable concentrations of Siromune® after dose adjustment or after loading dose due to the delay in reaching steady-state because of the prolonged half-life.
Method of administration
Siromune® is for oral use only.
Tablets should not be crushed, chewed or split.
To minimize variability, Siromune® should consistently be taken either with or without food.
Grapefruit juice should be avoided.
OVERDOSAGE
At present, there is minimal experience with overdose. One patient experienced an episode of atrial fibrillation after ingestion of 150 mg of Sirolimus. In general, the adverse effects of overdose are consistent with those listed in "Adverse effects". General supportive measures should be initiated in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of Sirolimus, it is anticipated that Sirolimus will not be dialyzable to any significant extent.
STORAGE CONDITIONS
Store below 25°C.
Keep in original pack in intact conditions.
Date of revision: May 2013.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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