

Sirolimus (*Rapamune*[®])

SCG: For Transplant patients

The following guidelines are designed to provide information relating to sirolimus and to outline the responsibilities of the primary and secondary care teams in the prescribing of sirolimus.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

Introduction:

Early attempts at organ transplantation without utilising immunosuppressive therapy proved unsuccessful and chemical immunosuppressive agents came into use in the early 1960's, increasing one-year survival rates. Major advances in transplantation were made following the introduction of ciclosporin-based immunosuppression, usually in combination with azathioprine and corticosteroids. The development of tacrolimus provided an alternative to ciclosporin but shares many of the same adverse effects that limit the use of ciclosporin.

Sirolimus (formerly known as rapamycin) is a naturally occurring macrolide antibiotic that exerts immunosuppressive effects through inhibition of T and B cell activity. Its mechanism of action is distinct from ciclosporin and tacrolimus and in contrast to these agents, sirolimus exhibited no apparent nephrotoxic properties or deleterious effects on blood pressure during clinical trials. It has also shown a synergistic effect when given in combination with ciclosporin and can exacerbate ciclosporin induced nephrotoxicity when used together.

RESPONSIBILITIES and ROLES

Specialist responsibilities (Transplant team):

1. Initially prescribe and stabilise the patient on the treatment regimen and monitor transplant graft function.
2. Measure sirolimus blood levels and advise changes of dose to patient and GP.
3. Provide patients with a current medication record book ("blue book").
4. Monitor efficacy of the treatment and side effects.
5. Provide access to back up and support facilities.
6. Evaluate any adverse events reported by the patient or GP (all potential adverse events should be reported to the CHM (MHRA), see side effects section).
7. Educate patients in knowledge of drug therapy to maximise compliance and be aware of when to seek medical attention.

General Practitioner's responsibilities:

1. Prescribe sirolimus maintenance therapy once the patient is stabilised on therapy and side effects have been excluded as far as possible by the hospital. Dosage instructions will be provided by the Transplant Unit.
2. Encourage patients to complete their daily medication record and document any changes to therapy in the "blue book".
3. Check for possible drug interactions when newly prescribing or stopping concurrent medication.
4. Report any suspected adverse events to the Transplant Unit.

Patient's role:

1. Take Sirolimus (*Rapamune*[®]) as prescribed and complete daily medication record in their "blue book".
2. Notify any adverse events to GP and Transplant Unit.
3. Notify use or intended use of over the counter (OTC) and herbal medications
4. Ensure they attend for monitoring as per shared care guideline.

BACK-UP ADVICE AND SUPPORT

Papworth Hospital Main Switchboard	01480 830541
Transplant Unit Reception	01480 830541 ext. 4455
Transplant Co-ordinator	page via switchboard 01480 830541
Pharmacy Medicines Helpline	01480 364739
Transplant Pharmacist	01480 830541 ext. 4762 (bleep 931)
Consultant Transplant Cardiologist	Dr Jayan Parameshwar Bleep 933 Dr Clive Lewis Bleep 842
Consultant Transplant Pulmonary Physician	Dr Jas Parmar Bleep 989

Out of hours, contact the on-call pharmacist via switchboard

Consultant and medical staff are always available to give advice and can be contacted through the main hospital switchboard

SUPPORTING INFORMATION

Licensed Indications:

Sirolimus is licensed for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended that Sirolimus be used initially in combination with ciclosporin microemulsion and corticosteroids for two to three months. Sirolimus may be continued as maintenance therapy with corticosteroids only if ciclosporin microemulsion can be progressively discontinued.^{1,2} It is not currently licensed for use in heart and lung, heart or lung transplants.

Dosage and Administration:

Sirolimus is administered usually on a once daily basis.

To minimise variability, patients should be instructed to take sirolimus consistently either with or without food and at the same time each day so that trough levels are representative of the true value when they return to hospital for monitoring blood levels. Patients are instructed not to take their sirolimus on the morning of their clinic visit until after their blood test so that blood levels taken represent trough concentrations.

If concomitantly on ciclosporin it is recommended that sirolimus be taken consistently 4 hours after the ciclosporin dose.¹

Some of our patients, especially those with cystic fibrosis may have impaired absorption leading to problems maintaining adequate immunosuppression levels.^{3,4} To further improve absorption pancreatic insufficient patients with cystic fibrosis are advised to take pancreatic enzyme supplements at the same time as their immunosuppression.

If the oral solution is used, the prescribed dose should be mixed with 60ml of water or orange juice in a plastic or glass container, stirred vigorously for one minute and then drunk. The container should then be refilled with at least 120mls of water or orange juice, stirred well and drunk immediately. No other liquids including grapefruit juice should be used for dilution.¹

Contraindications:

Hypersensitivity to sirolimus or any other of the excipients.

Therapeutic Use:

Sirolimus has been used in heart and lung transplant recipients at Papworth Hospital and in centres around the world for over ten years. There is now considerable evidence supporting its use as a calcineurin inhibitor sparing agent^{4,5} and as an agent to slow the progression of coronary artery disease in the transplanted heart.^{6,7} Based on the experience gained during this time, sirolimus is reserved for patients where standard immunosuppression is contra-indicated, not tolerated or ineffective, usually in combination with azathioprine or mycophenolate and/or corticosteroids. Its main role has been in patients who cannot take ciclosporin or tacrolimus due to nephrotoxicity.⁸

Side Effects:¹

All immunosuppressive agents are powerful and potentially toxic drugs, and therefore adverse events may be observed. Any potential adverse effect detected should be reported directly to the Transplant Unit - **it is vital that drug doses are not changed without first consulting the Transplant Unit.**

The following are the most commonly reported (occurring in >10% patients) adverse events that have been observed in patients taking sirolimus:

- Hypercholesterolaemia and hypertriglyceridaemia
- Thrombocytopenia and anaemia
- Acne
- Diarrhoea
- Arthralgia
- (Susceptibility to **infection** (bacterial, viral, fungal and protozoal) is increased in patients receiving immunosuppressive therapy).
- Interstitial pneumonitis and fibrosis
- Peripheral oedema
- Hepatotoxicity has been reported, the risk may increase as trough sirolimus levels increase
- Impaired wound healing following transplant surgery has been reported.

The above list of adverse events is not exhaustive and the summary of product characteristics Rapamune[®] and BNF should be consulted for a comprehensive list of adverse events.

As sirolimus is a recently launched medicine, it is therefore monitored intensively by the MHRA and ALL suspected reactions (including those considered not to be serious) should be reported through the Yellow Card Scheme www.yellowcard.gov.uk.

Monitoring:

Doses are individualised based on whole blood trough concentrations. Aim for a trough level of 10 to 15microgram/L year one post transplant and 5 to 10microgram/L in long-term patients.⁹ Steady-state drug concentrations are reached approximately 5 to 7 days after initiation of treatment or dose adjustment. Dose adjustment is not required in renal impairment but sirolimus levels should be monitored closely in patients with mild or moderate hepatic impairment.

Secondary Care (at each Outpatient Clinic appointment):

- Sirolimus trough levels
- Blood urea and electrolytes to monitor renal function
- Liver function tests
- Compliance with medication regime
- Blood pressure
- Monitor for drug interactions.

Primary Care:

- Blood urea and electrolytes to monitor renal function every three months (this may have already been done at Outpatient Clinic depending on frequency of appointments)
- Liver function tests every three months (this may have already been done at Outpatient Clinic depending on frequency of appointments)
- Blood pressure
- Monitor for drug interactions
- Take blood sample for sirolimus level (trough) on written request of the Transplant Unit.

Drug Interactions:¹

Many drugs, including sirolimus, are metabolised via the microsomal cytochrome P-450 enzyme system in the liver and in the intestinal wall. Some drugs have the effect of inhibiting P-450 thereby increasing available sirolimus in the blood to potentially toxic levels.

Other drugs can induce the P450 enzyme system promoting the metabolism of sirolimus to sub therapeutic levels. Sirolimus is also a substrate for the multi-drug efflux pump, P-glycoprotein (P-gp) located in the small intestine; therefore inhibitors of P-gp may decrease the efflux of sirolimus from the intestinal walls and increase sirolimus levels. Herbal medicines can also affect sirolimus efficacy either by direct effect on the P-450 system or indirectly by antagonising the immunosuppressant effect of sirolimus (eg echinacea).

For advice on sirolimus interactions please do not hesitate to contact the pharmacy Medicines Information Department. The following list is not exhaustive and the summary of product characteristics and BNF should be consulted for a comprehensive list of drug interactions.

1. **Drugs which may decrease sirolimus levels:**
rifampicin, carbamazepine, phenobarbitone, phenytoin, rifabutin, St. John's Wort,
2. **Drugs which may increase sirolimus levels:**
ciclosporin, ketoconazole, danazol, nifedipine, verapamil, fluconazole, itraconazole, clotrimazole, clarithromycin, erythromycin, troleandomycin, metoclopramide, bromocriptine, cimetidine, protease inhibitors, voriconazole, posaconazole.
3. Sirolimus may increase mycophenolic acid levels leading to increased incidence of neutropaenia. Monitor for neutropaenia. The transplant centre may reduce mycophenolate dose when Sirolimus is commenced.

NB

- Vaccines may be less effective in immunocompromised patients.
- Live vaccines should be avoided.
- Grapefruit juice affects cytochrome P450 mediated metabolism of sirolimus and should therefore be avoided

Cost:

Funding of medicines for cardiothoracic transplantation outside the hospital setting, whether pre or post transplant is the responsibility of the patient's Primary Care Trust. As directed by the Department of Health National Specialist Commissioning Advisory Group (NSCAG) in August 2002, PCTs need to ensure that funding for post transplant drug treatment is made available for patients. As soon as a GP is made aware of a patient requiring an expensive medicine, they are advised to discuss the funding mechanisms for it with their PCT prescribing manager.

Availability:

Sirolimus is available as 1mg and 2 mg film coated tablets and 1mg/ml oral solution, which can be ordered from wholesalers and is usually available within 24 hours. We recommend that patients are prescribed the 1mg tablet as changes in dose are easier to institute (average dose 1 to 2mg per day). Sirolimus liquid must be kept refrigerated and tablets protected from light.¹

References:

1. Summary of Product Characteristics Rapamune[®]. Accessed via www.medicines.org.uk on 10/06/2010. Last updated 12/02/2010.
2. British National Formulary. Number 59. March 2010.
3. Deierhoi MH *et al.* Review of select transplant subpopulations at high risk of failure from standard immunosuppressive therapy. *Clinical Transplantation*. 2000; 14(5): 439-448.
4. Knoop C *et al.* Ciclosporin pharmacokinetics and dose monitoring after lung transplantation: comparison between cystic fibrosis and other conditions. *Transplantation*. 2003; 76(4): 683-688.
5. Groetzner J *et al.* Mycophenolate mofetil and sirolimus as calcineurin inhibitor-free immunosuppression for late cardiac transplant recipients with chronic renal failure. *Transplantation*. 2004; 77(4): 568-74.
6. Kushwaha SS *et al.* Sirolimus in cardiac transplantation: use as a primary immunosuppressant in calcineurin inhibitor induced Nephrotoxicity. *JHLT*. 2005; 24(2): 2129-36.
7. Mancini D *et al.* Use of Rapamycin slows progression of cardiac transplantation vasculopathy. *Circulation*. 2003; 108 (1): 48-53.
8. Segovia J *et al.* Treatment of Allograft vasculopathy in heart transplantation. *Expert Opin Pharmacotherapy*. 2006; 7 (17): 2369-83.
9. Guidelines for the management of the transplant patient. Papworth Hospital NHS Trust document DN215. Revised October 2009.

These guidelines were:

Originated and approved by Drugs and Therapeutics Committee: September 2006

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