

Produced by the
UK Medicines Information Pharmacists Group

NEW MEDICINES ON THE MARKET

Evaluated information for the NHS

Sirolimus

Summary

- Sirolimus is a new immunosuppressive for use in renal transplantation. It is used initially in combination with ciclosporin and corticosteroids, but it may be continued as maintenance therapy with corticosteroids only if ciclosporin can be discontinued.
- When used in this way, sirolimus appears to be associated with a low rate of rejection and good renal function up to twelve months post-transplantation. However, this is based on studies comparing two sirolimus-containing regimens – one in which ciclosporin was continued in combination with sirolimus and corticosteroids, and another in which the ciclosporin was discontinued. These studies have not yet been published in full. There have been no direct comparisons of the licensed regimen (with ciclosporin elimination) versus standard ciclosporin- or tacrolimus-based regimens.
- Sirolimus has a different adverse effect profile to the calcineurin inhibitors – ciclosporin and tacrolimus. Importantly, it lacks significant nephrotoxicity. It is hoped that by reducing exposure to nephrotoxic drugs, outcome will be improved in the long-term. Long-term data from clinical trials are lacking at present.
- The licensed indications are limited to use in patients at low to moderate immunological risk. There are insufficient data on its use in high-risk patients *e.g.* those with high serum panel reactive antibody titre (>75%).
- It is difficult to judge the cost implications of introducing sirolimus as dosages of the main immunosuppressants are individualised and highly variable. Drug costs may be increased if it is replacing ciclosporin standard triple regimens, but the impact will be less if tacrolimus-based regimens are replaced with sirolimus/ciclosporin.

Date Published: August 2001

Monograph Number: 4/01/08

Marketed: March 2001

Region of origin to whom queries should be directed: London (South Thames)

The information contained in this document will be superseded in due course.
Not to be used for commercial purposes
Copyright MIPG 2001

Web site <http://www.ukdipg.org.uk/stage4.htm>

Sirolimus

Approved Name:	Sirolimus
Brand Name (Manufacturer):	Rapamune® (Wyeth Europa Ltd)
Presentation:	Oral solution 1mg/mL
BNF Therapeutic Class:	8.2.2 – Corticosteroids and other immunosuppressants.
Licensed Indications:	Prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is used initially with ciclosporin and corticosteroids for 2–3 months. Sirolimus may be continued as maintenance therapy with corticosteroids only if ciclosporin can be discontinued.
Dosage and Administration:	See Summary of Product Characteristics (SPC) [1]. <i>Initial Therapy:</i> 6mg loading dose, followed by 2mg daily, then adjusted to give whole blood trough levels of 4-12ng/mL. Sirolimus should be combined with a tapering regimen of corticosteroids and ciclosporin. <i>Maintenance:</i> Ciclosporin should be discontinued over 4-8 weeks and the sirolimus dose increased to give whole blood trough levels of 12-20ng/mL (ranges based on chromatographic assay – gives results approximately 20% lower than immunoassay)
Sector of Use:	Hospital [Y] Primary Care [Y]

Therapeutic Comment:	The recommended regimen [1], appears to be associated with a low rate of rejection and good renal function up to twelve months post-transplantation. However, this is based on unpublished studies comparing two sirolimus-containing regimens. There are no direct comparisons of the licensed regimen with standard ciclosporin/tacrolimus-based regimens.
-----------------------------	--

Cost and Course Details:	The dose of sirolimus is adjusted individually, and is lower when used in combination with ciclosporin. At an <i>initial</i> dose of 2mg daily, 28 days' treatment costs £138.32. At a <i>maintenance</i> dose of, for example, 6mg daily, 28 days' treatment costs £414.96 (<i>MIMS, July 2001</i>)
---------------------------------	--

Treatment Alternatives: Standard regimens consist of ciclosporin *or* tacrolimus and corticosteroids, with or without azathioprine. Doses of ciclosporin and tacrolimus are individually adjusted. The doses given below are examples only. Mycophenolate mofetil is licensed as an adjunct to ciclosporin and corticosteroids.

Drug	Daily dose	Cost/28 days
Ciclosporin <i>Neoral</i> ® capsules	275mg o.d.	£199.19
Tacrolimus <i>Prograf</i> ® capsules	4 mg b.d.	£416.32
Mycophenolate mofetil <i>CellCept</i> ® capsules	1g b.d.	£254.03
Azathioprine tablets	150mg o.d.	£12.99

Costs from MIMS and Drug Tariff, July 2001

Sirolimus

INTRODUCTION

In the UK and Republic of Ireland, an average of 1836 cadaveric and living donor renal transplants were performed annually between 1991 and 2000 [2]. Maintenance immunosuppressive therapy is used after transplantation to prevent acute rejection. This occurs in approximately one half of renal transplants despite immunosuppression with standard regimens. Most episodes occur in the first six months and respond to treatment. However, acute rejection remains the major cause of graft-loss in the first year [3]. Also, there is an association between the incidence of acute rejection and the subsequent development of chronic rejection, the commonest cause of failure of long-term allografts [4,5].

Until recently, the choice of immunosuppressants was limited. The calcineurin inhibitors, first ciclosporin and more recently tacrolimus, have formed the mainstay of treatment. However their benefits are limited by nephrotoxicity [6]. Patients are usually treated with a combination of a calcineurin inhibitor and corticosteroids, with or without concomitant azathioprine or mycophenolate mofetil.

Sirolimus is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant (there are insufficient data on high-risk patients). It is used initially in combination with ciclosporin and corticosteroids. Subsequently, sirolimus may be used as maintenance therapy, but only if ciclosporin can be progressively discontinued. Its main advantage over calcineurin inhibitors is its lack of nephrotoxicity. Nephrotoxicity is thought to contribute to the development of long-term graft failure, although its role is unclear.

PHARMACOLOGY

Sirolimus is a macrolide antibiotic with immunosuppressant activity. It is structurally related to tacrolimus, although its mechanism of action is different. While ciclosporin and tacrolimus block T-cell cycle progression at the G₀ (quiescent) to the G₁ stage (growth phase), sirolimus prevents cells progressing from the G₁ to the S phase (the phase when DNA is replicated) [7]. Sirolimus blocks T-cell activation by interleukin-2, -4, and -6, and stimulation of B-cell proliferation by lipopolysaccharide. Sirolimus directly inhibits B-cell immunoglobulin synthesis caused by interleukins.

Sirolimus only becomes active after forming a complex with intracellular binding proteins known as immunophilins. Both sirolimus and tacrolimus bind to the same family of immunophilins called the FK-binding proteins. However, sirolimus does not act by inhibition of calcineurin. Instead, the sirolimus-FK-binding protein complex inhibits 'target of rapamycin' proteins (TOR-1 and -2) – phosphatidylinositol kinase homologues required for cell-cycle progression in response to cytokines such as interleukin-2 (IL-2) [3].

PHARMACOKINETICS

See Summary of Product Characteristics (SPC) [1].

EFFICACY

The outcomes of most interest when evaluating post-transplant immunosuppressive therapy are graft and patient survival. However, since success rates at one year are high with current regimens, it is difficult to show a significant improvement in these endpoints. Because of this, agents are usually evaluated against the endpoint of biopsy-proven acute rejection within the first six months to one year post transplantation. Biopsy

Sirolimus

is required to differentiate between acute rejection and other problems, such as nephrotoxicity.

Acute rejection is an important endpoint in itself – hospitalisation is required, and although it can usually be overcome with high-dose corticosteroids, if these are ineffective, other options such as antilymphocyte preparations are needed. These treatments are associated with increased risk of infection and malignancy [3]. Acute rejection in the first year is also associated with a detrimental effect on long-term graft survival [5].

There are no published trials evaluating sirolimus in the regimen recommended in the SPC [1]. The main *published* evidence comes from two large multicentre trials, one carried out in the USA [8] and one international study [9] (see table). In these studies, sirolimus was used at fixed doses rather than being adjusted against blood levels, and in neither study was there any attempt to withdraw ciclosporin in the sirolimus group.

In both studies, sirolimus 2mg or 5mg daily was used as an adjunct to ciclosporin and corticosteroids. In the US study, which compared sirolimus with azathioprine, sirolimus 2mg daily was found to reduce the incidence of biopsy-confirmed acute rejection at six months by 43% and 5mg daily by 60% relative to azathioprine (rates of 16.9% and 12.0% respectively versus 29.8% for azathioprine). In the international study, where the comparator was placebo, the efficacy was similar with 40% and 54% reductions in the risk of acute rejection at six months (rates of 24.7% and 19.2% for the higher and lower dose respectively, versus 41.5% for placebo). However, there was no difference between the two drugs in terms of graft or patient survival, which – as may be anticipated – were high in both groups.

The European Public Assessment Report (EPAR) mentions two unpublished studies in which sirolimus was used in a regimen similar to that finally recommended [10]. The larger (n = 525) is an ongoing trial, which will continue up to 5 years (12-month data are cited in the EPAR). For the first three months, all patients received ciclosporin, sirolimus, and corticosteroids. Patients who met the inclusion criteria (no severe immunological or vascular rejection during the last 4 weeks, serum creatinine <400micromol/L, and sufficient renal function to support ciclosporin withdrawal according to investigator's discretion) were then assigned to one of two groups – Group A: ciclosporin reduced to target trough concentration 75-200ng/mL plus sirolimus 2mg/day, adjusted to targeted trough concentration >5ng/mL or Group B: ciclosporin tapered to discontinuation plus sirolimus increased to targeted trough concentration (20-30ng/mL by immunoassay, or 15-25ng/mL by chromatographic assay).

Four-hundred and thirty patients were randomised. The cumulative incidence of acute rejection was larger in the ciclosporin withdrawal group – group B – (20% at twelve months versus 13.5% in Group A) but this did not reach statistical significance ($p = 0.093$; Fisher's exact test). This was attributed to a transient increase in rejection during the period of ciclosporin tapering. However, from month 6 onwards, renal function (mean calculated GFR) was significantly better in the ciclosporin withdrawal group.

In the smaller phase II study (n = 246) [10,11] patients who had established graft function by seven days post transplantation were randomised to fixed-dose sirolimus 2mg/day plus continued ciclosporin, or sirolimus 20mg/day for three days, 10mg/day on days 4-9 then adjusted to target trough levels of 10-20ng/mL (by

Sirolimus

immunoassay, equivalent to 8-16ng/mL by chromatographic assay) while ciclosporin was continued for the first two months, then tapered to discontinuation during month three. One-hundred and ninety seven patients were randomised [11]. The primary endpoint was graft function in the “efficacy population”, defined as those who were on the assigned therapy and had not suffered an acute rejection episode since transplantation. Patients in the ciclosporin discontinuation group who met these criteria had, on average, better graft function than the group who continued both drugs. Acute rejection, a secondary endpoint, was similar in both groups.

Further evidence for the efficacy of sirolimus maintenance without concurrent ciclosporin comes from two trials in which sirolimus was compared with ciclosporin (in combination with corticosteroids and either azathioprine [12] or mycophenolate mofetil [13]). In both studies, the efficacy of sirolimus in preventing rejection was similar to that of ciclosporin. Sirolimus was also associated with better renal function (higher GFR) than ciclosporin, although this was not statistically significant overall (the difference only achieved statistical significance at two time points).

ADVERSE EFFECTS

The adverse effect profile of sirolimus differs from ciclosporin and tacrolimus. Its main advantage is that it appears to lack significant nephrotoxicity. Lymphocele, hypercholesterolaemia, hypertriglyceridaemia, peripheral oedema, leukopenia and thrombocytopenia are the most common adverse effects identified in the clinical studies.

Patients on any immunosuppressive therapy are predisposed to infections, and are at increased risk of neoplasia and post-transplant lymphoma.

CONTRAINDICATIONS AND PRECAUTIONS

See SPC [1]. Sirolimus has been administered with ciclosporin, azathioprine, mycophenolate mofetil, corticosteroids, and cytotoxic antibodies in clinical trials. Co-administration with other immunosuppressive agents has not been extensively investigated.

Pharmacokinetics have not been studied in patients with severe hepatic impairment, it is recommended that sirolimus whole blood trough levels be closely monitored in hepatically impaired patients.

Co-administration of sirolimus with strong inducers or inhibitors of CYP3A4 is not recommended unless the benefit outweighs the risk. Sirolimus levels should be closely monitored.

The SPC recommends *Pneumocystis carinii* prophylaxis for the first 12 months following transplantation, and cytomegalovirus (CMV) prophylaxis for 3 months after transplantation, particularly for patients at increased risk for CMV disease [1]. At present, most transplant centres have their own policies regarding *Pneumocystis carinii* and CMV prophylaxis, and these vary. Co-trimoxazole may be given to all patients, or just to those receiving additional immunosuppression, e.g. antilymphocyte antibodies. CMV prophylaxis is generally only given to patients considered to be at high risk, e.g. CMV seronegative recipients of organs of seropositive donors, or seropositive recipients who have received an antilymphocyte antibody preparation.

Patients should be monitored for hyperlipidaemia. Limited data suggest that concomitant administration of HMG-CoA reductase inhibitors and/or fibrates is well tolerated.

REFERENCES

1. Summary of Product Characteristics - Rapamune. Wyeth Europa Ltd. 2001.
2. United Kingdom Transplant Support Service Authority. Yearly transplant statistics for the UK and Republic of Ireland as recorded by UK Transplant. 2001. Available from URL <http://www.uktransplant.org.uk/pdf/YearlyTxStats.pdf> – last visited 23rd July 2001
3. Perico N, Remuzzi G. Prevention of transplant rejection: current treatment guidelines and future developments. *Drugs* 1997; **54**: 533-70
4. Suthanthiran M, Strom TB. Medical progress: Renal transplantation. *N Engl J Med* 1994; **331**: 365-375
5. Hariharan S, Johnson CP, Bresnahan BA, *et al.* Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000; **342**: 605-12
6. Saunders RN, Metcalfe MS, Nicholson ML. Rapamycin in transplantation: a review of the evidence. *Kidney Int* 2001; **59**: 3-16
7. Gregory CR. Immunosuppressive approaches to the prevention of graft vascular disease. *Transplant Proc* 1998; **30**: 878-80
8. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. The Rapamune US Study Group. *Lancet* 2000; **356**: 194-202
9. MacDonald AS. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation* 2001; **71**: 271-80
10. European public assessment report (EPAR): Rapamune. Committee for Proprietary Medicinal Products. 2001.
11. Hricik D. Improved renal function with cyclosporine elimination in sirolimus-treated renal transplant recipients: one-year results from a phase II trial. *Transplant 2001 Chicago IL*. May 11th – 16th 2001. Abstract 54
12. Groth CG, Backman L, Morales JM, *et al.* Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. *Transplantation* 1999; **67**: 1036-42
13. Kreis H, Cisterne JM, Land W *et al.* Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. *Transplantation* 2000; **69**: 1252-60

Sirolimus

Table 1: Studies of sirolimus in combination with ciclosporin and corticosteroids.

Ref	Design of Study (Publication Type)	Treatments Assessed	Primary Outcome Measure	Results and Comments
[8]*	Randomised, double-blind trial (n = 719). Patients were randomised in a 2:2:1 ratio to the two sirolimus dose levels and to azathioprine respectively.	Sirolimus 2mg or 5mg daily versus azathioprine 2-3mg/kg/day. Both groups received concomitant ciclosporin and corticosteroids.	Efficacy failure at 6 months, defined as the first occurrence of biopsy-confirmed acute rejection, functional or physical graft loss, loss to follow up, or death.	Rates of efficacy failure were significantly lower in the sirolimus 2mg and 5mg groups (18.7% and 16.8% respectively) than in the azathioprine group (32.3%). Analysis was by intention to treat
[9]*	Randomised, double-blind trial (n = 576). Patients were randomised in a 2:2:1 ratio to the two sirolimus dose levels and to placebo respectively.	Sirolimus 2mg or 5mg daily versus placebo. Both groups received concomitant ciclosporin and corticosteroids.	Efficacy failure at 6 months, defined as the first occurrence of biopsy-confirmed acute rejection, functional or physical graft loss, or death.	Rates of efficacy failure were 30.0% and 25.6% in the sirolimus 2mg and 5mg groups respectively, versus 47.7% in the placebo group. The efficacy failure rates in the sirolimus groups were significantly lower than in the placebo group. Analysis was by intention to treat.
Study 212-GL [10,11]	Randomised, open-label trial (n = 246). Patients who had established graft function by seven days post transplantation were randomised (n = 197).	Sirolimus 2mg/day plus continued ciclosporin, versus concentration-controlled sirolimus with ciclosporin tapered to discontinuation.	Graft function in the "efficacy population" – those who were on assigned therapy and had not suffered an acute rejection episode since transplantation.	At 12 months, renal function was better in the ciclosporin elimination group than in those who continued to receive ciclosporin. Serum creatinine was 135.3µmol/L versus 169.7µmol/L (1.53mg/dL vs. 1.92mg/dL, p = 0.002) and calculated GFR was 68.3mL/min versus 55.6mL/min, respectively (p < 0.001).
Study 310-GL [10]	Randomised, open-label trial (n = 525). All initially received sirolimus, ciclosporin and corticosteroids. Patients who fulfilled inclusion criteria (see text) were randomised at month 3 (n = 430).	Sirolimus 2mg/day plus ciclosporin at a reduced dose, versus concentration-controlled sirolimus with ciclosporin tapered to discontinuation	Graft survival.	At 12 months the incidence of acute rejection was 20.0% versus 13.5%, graft survival was 97.7%, versus 95.8% and patient survival was 98.1% versus 97.2% in the sirolimus-plus-ciclosporin and sirolimus (ciclosporin withdrawal) groups respectively. These differences were not statistically significant.

* Neither of these studies was powered to show a difference between sirolimus 2mg and 5mg for the primary endpoint.

Table 2: Sirolimus versus ciclosporin.

Ref	Design of Study (Publication Type)	Treatments Assessed	Primary Outcome Measure	Results and Comments
[12]	Randomised, open-label, parallel group (n = 83). All received azathioprine and corticosteroids.	Sirolimus (loading dose of 16-24mg/m ² /day followed by 8-12mg/m ² /day until day 7-10, then adjusted to whole blood trough levels of 30ng/mL for 2 months and 15ng/mL thereafter) versus ciclosporin (initially of 10mg/kg/day, then adjusted to whole blood trough levels of 200-400ng/mL for 2 months, and 100-200ng/mL thereafter).	Acute rejection, graft loss and death.	At 12 months, rates of acute rejection were similar in both groups (41% for sirolimus versus 38% for ciclosporin). There was one graft loss in the sirolimus group (due to acute rejection and sepsis), and there were three graft losses due to thrombosis, and one death due to pulmonary embolism (on day 367) in the ciclosporin group.
[13]	Randomised, open-label, parallel group (n = 78). All received mycophenolate mofetil for up to 6 months, and corticosteroids.	Sirolimus (loading dose of 24mg/m ² , then 24mg/m ² for 2 days, followed by 12mg/m ² , then adjusted against whole blood trough levels as above) versus ciclosporin (initial doses as per the site's usual practice, then adjusted against whole blood trough levels as above).	Biopsy-proven acute rejection.	At 12 months, the rate of biopsy-proven acute rejection was 27.5% in the sirolimus group, and 18.4% in the ciclosporin group, a difference of 9.1%; 95% confidence interval -9.45% to 27.6%. There were two sudden deaths in the ciclosporin group, and one patient in the sirolimus group died as a result of burns after being withdrawn from the trial. Graft survival was 92.5% and 89.5% in the sirolimus and ciclosporin groups respectively.