# National PBM Drug Monograph
# Sirolimus (Rapamune®)
### VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

## Introduction

Improvements in posttransplant care and immunosuppressive pharmacotherapy may be credited with the improvement in patient and graft survival following transplant. The armamentarium of immunosuppressive agents has grown significantly over the years, as well as the understanding of each agent's adverse effects and future areas for development. Sirolimus is a second-generation immunosuppressive agent, which provides an alternative to standard immunosuppressive regimens.

## Pharmacology/Pharmacokinetics[1,2,3]

The mechanism of action of sirolimus is distinct from that of the calcineurin inhibitors (CI), such as cyclosporine and tacrolimus, whose function is primarily dependent on the inhibition of cytokine gene expression. Sirolimus acts by binding the TOR protein kinases, which in turn prevents cell cycle progression by blocking the ability of T cells to proliferate in response to interleukin (IL)-2 stimulus.

Sirolimus is rapidly but poorly absorbed following oral administration with an approximate oral bioavailability of 15%. It reaches maximum blood concentrations in 0.5-2.3 hours after dosing. Its absorption is affected by high fat meals.

After absorption, sirolimus is rapidly distributed to the red blood cells. Approximately 95% of the drug is bound to red blood cells, with the agent's high lipophilicity simplifying this process. The binding to red blood cells may also account for the increased potency that sirolimus displays in comparison to cyclosporine.

Sirolimus is extensively metabolized by the hepatic CYP3A4 system and is also a substrate in the p-glycoprotein pump of the intestinal wall. The clearance of sirolimus is affected by both of these pathways and displays a large interpatient variability. The majority of the seven metabolites are formed via O-demethylation and hydroxylation. The metabolites account for less than 10% of the immunosuppressant activity of sirolimus. These metabolites are excreted in bile and feces. The half-life of sirolimus ranges from 57-62 hours, making once daily dosing feasible.

The therapeutic window of sirolimus may be relatively narrow. Therefore, optimal use of sirolimus requires careful attention to maintenance of therapeutic levels. Optimizing sirolimus serum concentrations at 15 ng/mL, lessens the occurrence of severe adverse reactions.

## FDA Approved Indication(s) and Off-label Uses[3]

Sirolimus is approved for prophylaxis of organ rejection following renal transplant and is recommended for combination use with cyclosporine and corticosteroids. Sirolimus has been used off-label for the treatment of psoriasis.

## Current VA National Formulary Status

Currently the National Formulary includes the following immunosuppressive oral preparations; prednisone, azathioprine, cyclosporine, cyclosporine microemulsion, mycophenolate mofetil and tacrolimus. The last four agents are listed as being considered for local or VISN restrictions and/or criteria for use.

## Dosage and Administration[1,2,3]

In de novo transplant recipients a loading dose of sirolimus three times the maintenance dose is employed. In renal transplant recipients the doses investigated and proven safe and effective are 6mg and 2 mg/day, respectively. This should be administered as soon as possible following transplantation. Loading doses of 15 mg with a maintenance dose of 5mg/day have also been proven safe and effective but have not shown improved efficacy over the 2 mg/day regimen, except in an African American population. In patients at least 13 years of age but weighing less than 40 kg the loading dose and maintenance dose should be adjusted to $3mg/m^2$ and $1mg/m^2$ , respectively. The oral solution and the oral tablet are interchangeable on a milligram to milligram basis, however, the clinical interchangeability may be variable.

In patients with mild to moderate hepatic impairment the maintenance dose should be decreased by 33%. No adjustment of the loading dose is required.

Therapeutic monitoring of sirolimus blood levels is recommended. Doses should be adjusted to maintain trough levels of 5 to 15 ng/ml. This range takes into account the increased incidence of adverse effects with levels greater than 15ng/ml and the linear relationship between dose and blood level. The availability of the assay may present problems for some institutions. The standard method is HPLC with an immunoassay available in some clinical trials.

Many immunosuppressant protocols use a regimen of cyclosporine, corticosteroids and sirolimus. Caution must be exercised due to a pharmacokinetic interaction between sirolimus and cyclosporine. The agents should be administered four hours apart because concomitant administration results in increased sirolimus associated adverse effects.

Food affects the absorption of sirolimus and patients should be cautioned to consistently take their medication in the same way, whether it is with or without food. The oral solution should be diluted with water or orange juice, stirred vigorously and the process repeated with an additional amount of water or orange juice to insure the full dosed is consumed.

## Adverse Effects (Safety Data)[1,2,3]

The most notable and concerning adverse effect of sirolimus is hyperlipidemia, involving both hypercholesterolemia and hypertriglyceridemia. This effect has occurred in the majority of clinical trials conducted with the agent. As a comparison, cyclosporine and tacrolimus cause hyperlipidemia at a rate of 20-40%. Pooled data from the two large Phase III trials of sirolimus demonstrate a dose dependent effect with hyperlipidemia occurring in 44%, and 34% of the 5 mg/day and 2 mg/day groups, respectively.

Additional reported adverse effects are bone marrow suppression and increased liver function tests. Thrombocytopenia may be of concern in liver transplant patients who have a preexisting thrombocytopenia.

In the Phase III trials of sirolimus, the following effects had a significantly higher incidence in the sirolimus group than in controls; lymphocele, rash, acne, hypertension, arthralgia, diarrhea, anemia and hypokalemia.

Sirolimus patients have not demonstrated significantly increased incidences of nephrotoxicity, neurotoxicity or diabetes.

## Precautions/Contraindications[1,2,3]

Photosensitivity may occur with the use of sirolimus. Patients should be cautioned to take protective measures against sunlight exposure until individual tolerance is determined.

As with other immunosuppressive agents, care should be exercised in therms of antimicrobial prophylaxis. Post transplant patients are more prone to develop cytomegalovirus and Pneumocystis carinii infections.

Since sirolimus is a macrolide antibiotic, care should be exercised in patients with a known hypersensitivity to other agents in this class.

## Drug Interactions[1,2,3]

Sirolimus is extensively metabolized by the cytochrome P450 system. Additionally, it is a substrate in p-glycoprotein pathway in the gut wall. Other agents, herbal, food and drug, which affect these systems, will likely effect sirolimus as well. Caution should be used when these types of agents are used in conjunction with sirolimus and dosages of the later adjusted accordingly. Agents which would likely increase sirolimus concentrations include: clarithromycin, erythromycin, diltiazem, azole antifungals, protease inhibitors, verapamil, cyclosporine and cimetidine. Agents that act as enzyme inducers, thus lowering sirolimus levels may include: carbamazepine, phenobarbital, phenytoin, rifampin, rifabutin, rifapentine and St. John's Wort. Concomitant use of HMG-CoA reductase inhibitors with sirolimus may increase the levels of the former and result in an increased incidence of myopathy or rhabdomyolysis.

## Clinical Efficacy

In the two, large Phase III trials conducted for sirolimus, a total of 1295 patients were randomized. The center locations included US and European facilities.[4,5] The primary outcome in these trials was a composite endpoint of six-month biopsy proven acute rejection, graft loss and patient death. Azathioprine was used as the comparator agent and no antibody induction was allowed. Results from these trials demonstrated that sirolimus decreased the incidence of acute rejection in comparison to azathioprine in renal transplant recipients. However, patient and graft survival were not different between the groups over the two years of the study. Four treatment groups were examined: sirolimus (2 mg/day), sirolimus (5 mg/day), AZA, and placebo. All participants were also treated with cyclosporine and prednisone. Notably, these were not concentration-controlled studies. There were no significant differences with regard to patient or graft survival in any of the groups, as has been the case in most of the recent immunosuppression trials. Pooled data from these trials showed an overall rejection rate of 43.8% in the placebo (dual therapy) group and 32.9% in the AZA group. In the sirolimus cohort, the lowest incidence of rejection (17.9%) occurred with the 5 mg/day sirolimus dose, a rate significantly better than the rate observed for AZA-treated patients. It should be noted that many protocols do not use azathioprine with mycophenolate mofetil being used instead. Had this been used as a comparator arm the results may have been different.

In comparator trials of cyclosporine and sirolimus, [6] sirolimus has shown to be as effective as cyclosporine in preventing acute rejection and maintaining patient and graft survival for one year. The concern arises with the side effect profile of sirolimus, with this group displaying significantly more thrombocytopenia and diarrhea. The sirolimus group maintained a higher level of renal function based on the glomerular filtration rate. They also displayed more hyperlipidemia, which resolved with treatment.

Sirolimus has been investigated as a therapy, which may result in corticosteroid or cyclosporine sparing, thus reducing the adverse effects of the later agents. There appears to be a synergistic action between sirolimus and cyclosporine, which would allow for a sparing effect when the two are used concurrently[7]. Tedesco and associates[8], maintained therapeutic doses of CsA in the immediate postoperative period, but tapered to trough levels of 100-200 ng/mL within 6 months in kidney transplant recipients receiving 2 mg/day of sirolimus. Compared with a control group of AZA-treated patients, there were no differences in renal function at 6 months posttransplantation.

These data support the general trend toward lowering the calcineurin inhibitor dosage when used in conjunction with sirolimus. These trials are relatively small and need to be supported with larger, randomized results.

Sirolimus has been investigated in other solid organ transplants. Since it has some antitumor effects, sirolimus may be beneficial to patients undergoing liver transplant for hepatocellular carcinoma. Four small trials have investigated sirolimus in liver transplant[1,9]. In a study by Kneteman, et al[13], eight patients received liver transplant as a result of hepatic malignancy. The patients initiated triple immunosuppressive therapy with corticosteroids, cyclosporine and sirolimus with a goal of reaching monotherapy with sirolimus. The results have only been reported in abstract form with an average follow up period of 11 months. No mortality had occurred by this time, four patients had experienced acute rejection, three during sirolimus therapy. Hyperlipidemia had developed in three patients. A trial of 15 liver transplant patients[14] randomized patients to receive sirolimus, cyclosporine and prednisolone or sirolimus and cyclosporine or sirolimus monotherapy. A caveat to this study was a 33% occurrence death. Many participants also developed infectious complications, likely due to triple immunosuppressive therapy. The authors concluded sirolimus has a role in therapy because it was well tolerated in the short followup period and provided appropriate immunosuppression without the use of steroids. The safety and efficacy of sirolimus in liver transplant needs to be confirmed with larger trials.

Sirolimus may possess characteristics that make it favorable for heart transplant recipients. In animal models sirolimus has been shown to significantly decrease intimal thickness, growth factors and cytokines. All of these are classic signs of chronic cardiac graft rejection. [10]

Most recently, sirolimus has been substituted or added to regimens (at first replacing either azathioprine or mycophenolate mofetil, but is now considered as an alternative to cyclosporine or even prednisone) for high-risk kidney transplant recipients (ie, with delayed graft function or high percent panel of reactive antibodies, retransplants, African Americans) and heart transplant recipients with pre-existing renal dysfunction. [11,12] In those who require early minimization of calcineurin inhibitor use, a number of centers are using induction therapy with OKT3 or one of the new interleukin-2 receptor antagonists, basiliximab or daclizumab.

## Current VA Prices

| trade_name | va_price | fss_price | va_ppu |
|---|---|---|---|
| NEORAL 100MG CAP | 111.23 | $130.42 | $3.7077 |
| NEORAL 25MG CAP | 27.9 | $32.64 | $0.9300 |
| SANDIMMUNE 100MG CAP | 127.36 | $156.76 | $4.2453 |
| SANDIMMUNE 25MG CAP | 32 | $39.27 | $1.0667 |
| GENGRAF 100MG CAPSULES | 66.06 | $66.06 | $2.2020 |
| CYCLOSPORINE 100MG CAP | 73.63 | $73.63 | $2.4543 |
| CYCLOSPORINE 100MG CAP | 121.55 | $121.55 | $4.0517 |
| CYCLOSPORINE 100MG/ML SOLN,ORAL | 170 | $170.00 | $3.4000 |
| GENGRAF 100MG/ML ORAL SOLN | 170 | $170.00 | $3.4000 |
| SANDIMMUNE | 208.49 | $239.64 | $4.1698 |
| GENGRAF 25MG CAPSULES | 16.53 | $16.53 | $0.5510 |
| CYCLOSPORINE 25MG CAP | 18.41 | $18.41 | $0.6137 |
| CYCLOSPORINE 25MG CAP | 30.75 | $30.75 | $1.0250 |
| SANDIMMUNE (FOR I.V. INFUSION)(250 | 173.25 | $219.77 | $3.4650 |
| CYCLOSPORINE 50MG/ML INJ | 195 | $195.00 | $19.5000 |
| NEORAL 100MG/ML ORAL SOLN | 202.81 | $236.94 | $4.0562 |
| RAPAMUNE 1MG TAB 10X10 | 388.44 | $388.44 | $3.8844 |
| RAPAMUNE 1MG TAB | 394.04 | $394.04 | $3.9404 |
| RAPAMUNE LIQUID | 233.13 | $233.13 | $3.8855 |

## Conclusion

The immunosuppressant class will most likely continue to grow. Recently, a second-generation TOR inhibitor, 40-0-[2-hydroxyethyl] rapamycin (also known as everolimus or RAD) has been tested in clinical trials. The characteristics of sirolimus make it an agent that should be considered in patients who may not tolerate current immunosuppressant regimens or develop rejection on current therapy regimens. The side effect profile is concerning, especially in patients who are more prone to develop hyperlipidemia or have pre-existing cardiac disease. Further trials are needed to more clearly define the position of sirolimus in transplant pharmacotherapy.

## References


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