Sirolimus (Rapamune ®)

Sirolimus (SRL) was registered for use as an anti-rejection therapy in Australia in 2002. Its immunosuppressive mechanism resides in its ability to block cytokine-simulated proliferation of T lymphocytes by interfering with their progression through the cell cycle. Sirolimus also has antiproliferative effects on a variety of other tissues and may affect wound healing and recovery from ATN.

Sirolimus may be used in the management of acute and chronic graft rejection, reducing the need for corticosteroids and cyclosporine. Due to its mode of action it can be complimentary to both CI’s and mycophenolate. The terminal half-life in stable renal transplant patients after multiple oral doses is 62+/−16 hours. The effective half-life however is shorter and mean steady-state concentrations are achieved after 5-7 days.

Dosing Monitoring

Sirolimus is available in 1 and 2mg tablets (these should not be crushed and 1mg/ml liquid solution. If being used in combination therapy with calcineurin, a 6mg loading dose (for patients greater than 40kg) is administered on the first day of treatment, and a maintenance dose of 2mg/day thereafter. The recommended maintenance dose for those less than 40kg is 1mg/m²/day, with adjustments made according to levels.

Note: If Sirolimus is used in conjunction with CyA the dose should be given 4 hours after the last dose of CyA.

Due to the long half-life of Sirolimus, trough levels accurately reflect exposure to the drug. A therapeutic trough level of 4-12ng/mL is recommended for patients receiving a calcineurin in combination therapy. For patients in whom a CI is not used, an initial trough level of 12 to 20 ng/mL is recommended. Trough level testing for Sirolimus is now done by SEALS based on an Immunoassay, which gives slightly higher levels than the previous HPLC method. The table below gives target levels by immunoassay.

Renal function should be monitored closely during concomitant administration of Sirolimus and calcineurin inhibitors (particularly CyA) because of potentiation of nephrotoxicity. Appropriate adjustment to the immunosuppressive regimen should be considered in patients with elevated serum creatinine levels.

For patients who are switched to Sirolimus due to intolerance of CI’s, a loading dose (depending on body size and time post-transplant) should be given on the morning after the last dose of the CI, which should then be discontinued. A maintenance dose should be commenced with a trough level to be taken on day 5-7 and as required until the desired trough level of has been reached. This abrupt switch avoids nephrotoxicity when used in combination with CNI and is associated with very low acute rejection rates following switch.

Target trough levels may be higher in individuals deemed to be at high risk e.g. rejection episode in last 3 months.

A table of recommended trough levels for patients on Sirolimus follows. Note that Immunoassay Tests have mostly replaced HPLC for sirolimus levels. The Immunoassay method is referred to below and reads about 20% higher than HPLC method.
### Sirolimus loading doses, maintenance doses and trough levels by patient type

<table>
<thead>
<tr>
<th>Time Post Transplant (months)</th>
<th>Loading Dose# Day 1</th>
<th>Initial Maintenance Dose Day 2 - 7</th>
<th>Target Trough level (first measure day 5 – 7, then weekly till steady state)</th>
<th>Maintenance trough level over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>8 – 10 mg</td>
<td>5 – 8 mg</td>
<td>12 – 18 ng/ml</td>
<td></td>
</tr>
<tr>
<td>3-12</td>
<td>8 – 10 mg</td>
<td>4 – 6 mg</td>
<td>10 – 15 ng/ml</td>
<td></td>
</tr>
<tr>
<td>&gt;12</td>
<td>8 – 10 mg</td>
<td>2 – 5 mg</td>
<td>5 – 10 ng/ml</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;12 and high immunological risk</td>
<td>8 – 10 mg</td>
<td>5 – 8 mg</td>
<td>10 – 18 ng/ml</td>
<td></td>
</tr>
</tbody>
</table>

# The last dose of the CNI to be taken on Day 0. The CNI dose is not taken on Day 1.

ŧFor very long stable patients the loading Dose may be omitted.

Immunoassay method ~ 20% lower with HPLC. Levels should be measured weekly until stable, then every 1 to 3 months thereafter. Since sirolimus has a long half-life (about 5 days) more frequent measurements of trough levels are unnecessary.

When adjusting the maintenance dose of SRL the following formula is used:
New Maintenance Dose = Current maintenance dose x (desired target level divided by current trough)

### Side Effects:
Hyperlipidaemia, lymphocele, peripheral oedema, anaemia, thrombocytopenia, acne, arthralgia, hypokalaemia, increased lactate dehydrogenase (LDH) and rarely aseptic pneumonitis.

### Drug Interactions:
Agents that increase Sirolimus levels: CYP3A4 inhibitors, cyclosporine, tacrolimus, diltiazem, nicardipine, verapamil, macrolide antibiotics, cisapride, metaclopromide, cimetidine, protease inhibitors, ketoconazole, danazol, erythromycin, bromocriptine and grapefruit juice.

**Acceptable calcium channel blockers are nifedipine and amlodipine.**

Agents that decrease Sirolimus levels: Rifampicin (CYP3A4 inducer), rifabutin, carbamazepine, phenobarbitone, phenytoin, octreotide (oral formulation only) and St John’s Wort.

**Mycophenolate/Azathioprine:** The use of sirolimus in combination with antiproliferative agents may cause myelosuppression and dose adjustment of both may be needed.

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