Sirolimus ORAL
Newborn Use Only

2024

<table>
<tr><td>Alert</td><td>Hazardous medication
National Institute for Occupational Safety and Health, USA (NIOSH) 2016 lists sirolimus in hazardous list of medicines - Increased risk of lymphomas and other malignancies; embryotoxic and fetotoxic.[22]
NIOSH recommends double chemotherapy gloves (e.g. purple Nitrile gloves), protective gowns and, if vomiting or potential spill is anticipated, eye/face protection.
Please refer to local policy on handling of hazardous medicines.
Immunosuppressant - Live vaccines should be avoided.</td></tr>
<tr><td>Indication</td><td>1. Congenital hyperinsulinaemic hypoglycaemia
2. Vascular anomalies, lymphatic, venous, and mixed lymphatic-venous malformation – Inclusive of Kaposiform Haemangioendothelioma (KHE) and Kasabach-Merritt phenomenon (KMP)
3. Cardiac rhabdomyoma</td></tr>
<tr><td>Action</td><td>Binds to specific cytosolic protein FKBP-12, and the subsequent FKBP-12-sirolimus complex inhibits the activation of the mammalian Target of Rapamycin (mTOR).[1]</td></tr>
<tr><td>Drug Type</td><td>Selective immunosuppressant agent.</td></tr>
<tr><td>Trade Name</td><td>Rapamune (Pfizer)</td></tr>
<tr><td>Presentation</td><td>1 mg/mL oral solution, 60mL bottle.</td></tr>
<tr><td>Dosage</td><td>
<table>
<tr><th>Days of life (irrespective of gestational age)</th><th>Dose</th><th>Interval</th></tr>
<tr><td>0 - 14 days of life</td><td>0.5 mg/m^2/day*</td><td>DAILY or in 2 divided doses at 12 hourly intervals. Measure trough concentrations (refer to monitoring section)</td></tr>
<tr><td>≥ 15 days of life</td><td>0.5-1 mg/m^2/day*</td><td>DAILY or in 2 divided doses at 12 hourly intervals. Measure trough concentrations (refer to monitoring section)</td></tr>
<tr><td>Beyond neonatal age group</td><td>Discuss with immunologist/haematologist/ subspecialist involved in the care</td><td></td></tr>
</table>
*Dose can be rounded as appropriate. Immunosuppressant - Live vaccines should be avoided.

Body Surface Area (BSA) calculation:
$$BSA\ (m^2) = \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}}$$
BSA calculator links:

https://amhonline.amh.net.au.acs.hcn.com.au/calculators/bodysurfacearea?menu=banner

https://www.pediatriconcall.com/calculators/body-surface-area-bsa-calculator, or

https://nicutools.org/#BSA</td></tr>
<tr><td>Dose Adjustment</td><td>Therapeutic hypothermia – Not applicable.
ECMO – No information.
Renal impairment – No dose adjustment.
Hepatic impairment – Discuss with pharmacist/immunologist/haematologist for any dose adjustment.</td></tr>
<tr><td>Maximum Dose</td><td>As per the immunologist/ haematologist.</td></tr>
<tr><td>Route</td><td>Oral or intragastric.</td></tr>
</table>

Preparation	Note: Dose volumes <0.1 mL can be inaccurate. **<u>Method 1 (for dose ≥100 microgram)</u>** 1. Use pre-prepared commercial 1 mg/mL oral solution. 2. Using appropriate PPE, remove the safety cap by squeezing the tabs on the cap and twisting counterclockwise. 3. Insert the oral syringe adapter (plastic tube with stopper provided in the carton) tightly into the bottle until it is even with the top of the bottle. 4. Withdraw the required dose using 1mL syringe. **<u>Method 2 (for dose <100 microgram)</u>** 1. Withdraw 1mL (=1mg) of pre-prepared commercial solution using 1mL syringe and transfer solution to an appropriate container. 2. Add 9mL of **MCT oil** (Medium chain Triglyceride oil) to make a final volume of 10 mL with a concentration of 100 microgram/mL. 3. Stir well and immediately draw up the required dose using 1mL syringe.
Administration	Oral - Stir and administer at once. Enteral feeding tube - Stir and administer at once. Flush the feeding tube after administration. **Note:** Administer consistently with or consistently without food to ensure the same amount is absorbed.
Monitoring	**Measure trough concentrations:** **0-14 days of life:** After 48 hours in preterm infants <37 weeks and after 72 hours in term infants, then weekly until steady state is achieved. **≥ 15 days of life:** After 48 hours in both preterm and term neonates, then weekly until steady state is achieved. **Optimal target trough concentration:** 10 ng/mL (5 - 15 ng/mL) but accept 5 – 9 ng/mL if clinical response is satisfactory. Subsequent trough levels dependent on progress and indication for treatment. Full blood count, renal function test, electrolytes, liver function test, triglycerides, lipid profile at regular intervals.
Contraindications	Known hypersensitivity to sirolimus or its derivatives or any of the excipients (ethanol).
Precautions	Hepatic impairment: Consider dosage reduction.
Drug Interactions	Affected by Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp): Examples of CYP3A4 inhibitors: Fluconazole, clarithromycin, erythromycin, ciclosporin. Substances of CYP3A4 inducers: Phenobarbital, phenytoin, rifampicin.
Adverse Reactions	Increased risk of bacterial and viral infections Mouth ulcers, constipation, diarrhoea, difficult healing, hyperglycaemia, acne, elevated liver gamma-glutamyl and aminotransferase, hypertriglyceridaemia, hypercholesterolaemia Vaccination may be less effective. Live vaccines should be avoided.
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Once bottle is opened: Contents should be kept refrigerated at 2°C to 8°C and used within one month. May develop a slight haze when refrigerated; this haze does not affect the quality of the product. If such haze occurs, allow the product to stand at room temperature and shake gently until the haze disappears.
Storage	Store at 2°C to 8°C. Refrigerate. Do not freeze. Protect from light.
Excipient	Polysorbate 80: known to increase the rate of di-(2- ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC). Phosal 50 PG (soy phosphatidylcholine - hydrogenated, propylene glycol, mono- and di-glycerides, ethanol, and ascorbyl palmitate).
Special Comments	Vaccination: Vaccination may be less effective. Live vaccines should be avoided.
Evidence	**Overview** Sirolimus is a selective immunosuppressant agent. Sirolimus inhibits T cell activation induced by most stimuli by blocking calcium-dependent and calcium-independent intracellular signal transduction.

Experimental evidence suggests that sirolimus binds to the specific cytosolic protein FKBP-12 and that the FKBP-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 the 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. It was mainly used for the prophylaxis of organ rejection in patients at mild to moderate immunological risk of receiving a renal transplant.[1]

Efficacy

Congenital hyperinsulinism: Based on a 5-year follow-up study in the UK evaluating the efficacy and complications of sirolimus used in children with hyperinsulinemic hypoglycaemia involving 22 patients with gestational ages ranging from 33 to 40 weeks, sirolimus can be considered for the treatment of congenital hyperinsulinism that was not responsive to diazoxide and octreotide.[4] Most reported cases have been for diffused disease, and sirolimus was started as an attempt to avoid total pancreatectomy. Other case series and reports suggested that successful glycaemic control can be achieved after the addition of sirolimus for around 3 to 6 weeks.[5-8]

Vascular anomalies, lymphatic, venous, and mixed lymphatic-venous malformation: Regarding Kaposiform Haemangioendothelioma (KHE) and Kasabach-Merritt phenomenon (KMP), sirolimus can be considered in the neonatal period if early treatment of KHE and KMP is warranted. A case report from USA documented successful treatment in an extremely preterm 26 weeks gestation baby with a weight of 590g.[9] Other case series and reports on clinical response include decrement in size of vascular tumour, and stabilisation of haematological and coagulation parameters.[10,11] Median response time was around 14 days to 4 weeks based on case series and reports from California, US, 5 from Netherlands and 1 from USA.[10,12]

Lymphatic malformations are associated with dysregulation of phosphatidylinositol 3-kinase (PI3K)/ AKT signalling pathway that is involved in cell mortality, proliferation, angiogenesis, and lymphangiogenesis. Inhibition of this pathway by sirolimus demonstrates antiproliferative properties in lymphatic vascular malformations.[13] Sirolimus has been used for upper airway lymphatic malformation in a Spanish case series of 7 patients ranging from gestational age of 34 to 39 weeks.[14] Other case reports include a term baby with cystic hygroma and diffuse lymphangiomatosis in Italy,[15] a term baby with venolymphatic malformation over the left periorbital region with thrombocytopenia in US,[16] and a preterm 32 weeks gestation baby with central conducting lymphatic anomaly in Australia.[23]

Cardiac rhabdomyomas: There are case reports reporting regression of cardiac rhabdomyomas with sirolimus therapy for neonates at risk of haemodynamic complications.[17] Responses have been noted after 5 to 15 days of commencement.[18-20] This included a 28 weeks preterm and commenced on sirolimus on Day 13 of life due to hemodynamic instability secondary to increasing subaortic rhabdomyoma.[19] There was an Australian case report of a 33 weeks gestation neonate, commenced on sirolimus on day 3 of life,[18] and there are other case reports on success in term babies.[17.20]

Co-administration with co-trimoxazole: There are case reports of prophylaxis with co-trimoxazole during sirolimus therapy in preterm and term babies.[19,20]

Safety

Sirolimus therapy in neonates has been associated with transient increase in liver transaminases[6,8] cholesterol, and triglyceride levels.[7,8]

In the UK 5-year follow-up study involving 22 patients with hyperinsulinemic hypoglycemia, viral and bacterial infections have been reported as one of the causes of cessation of sirolimus therapy.[4] Other possible adverse effects included hyperglycaemia, diarrhoea and difficult healing after an extravasation injury.[4]

Sirolimus may be diluted with MCT oil to achieve the necessary volume required for satisfactory administration for smaller babies.[21]

Pharmacokinetics

Sirolimus clearance estimates in neonates and infants showed an increment over time, attributable to the effect of body size, growth, and weight gain. Age-dependent changes in physiological parameters such as protein expression level of drug metabolic enzymes have been investigated to explain pharmacokinetic profiles in children.[2] The developmental changes in clearance are considered to be the result of the maturation of cytochrome P450 (CYP) 3A subfamilies in the liver and intestine, as sirolimus is

	predominantly metabolised by CYP3A4 and 3A5. Preterm babies would require special attention, as full-term babies of similar postnatal age may differ in drug elimination capacity.[3]
References	1. Australian Product Information RAPAMUNE® (sirolimus) Date of Revision 9th February 2022. 2. Emoto C, Fukuda T, Mizuno T, Schniedewind B, Christians U, Adams DM, Vinks AA. Characterizing the Developmental Trajectory of Sirolimus Clearance in Neonates and Infants. CPT Pharmacometrics Syst Pharmacol. 2016 Aug;5(8):411-7. 3. Mizuno T, Fukuda T, Emoto C, Mobberley-Schuman PS, Hammill AM, Adams DM, Vinks AA. Developmental pharmacokinetics of sirolimus: Implications for precision dosing in neonates and infants with complicated vascular anomalies. Pediatr Blood Cancer. 2017 Aug;64(8). 4. Maria G, Antonia D, Michael A, Kate M, Sian E, Sarah FE, Mehul D, Pratik S. Sirolimus: Efficacy and Complications in Children With Hyperinsulinemic Hypoglycemia: A 5-Year Follow-Up Study. J Endocr Soc. 2019 Feb 7;3(4):699-713. 5. Panigrahy N, Chirla DK, Bagga N, Gunda RK, Sukhija B, Reddy L. Sirolimus in infants with congenital hyperinsulinism (CHI) - a single-centre experience. Eur J Pediatr. 2022 Jan;181(1):407-412. 6. Hashemian S, Jafarzadeh Esfehani R, Karimdadi S, Vakili R, Zamanfar D, Sahebkar A. Clinical Efficacy Evaluation of Sirolimus in Congenital Hyperinsulinism. Int J Endocrinol. 2020 Jul 22;2020:7250406. 7. Méder Ü, Bokodi G, Balogh L, Körner A, Szabó M, Pruhova S, Szabó AJ. Severe Hyperinsulinemic Hypoglycemia in a Neonate: Response to Sirolimus Therapy. Pediatrics. 2015 Nov;136(5):e1369-72. 8. Senniappan S, Alexandrescu S, Tatevian N, Shah P, Arya V, Flanagan S, Ellard S, Rampling D, Ashworth M, Brown RE, Hussain K. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. N Engl J Med. 2014 Mar 20;370(12):1131-7. 9. Koury J, Brown M, Sturtevant S, Wiley C, Felton L. Use of Sirolimus in a Premature Neonate With Kaposiform Hemangioedema. J Pediatr Pharmacol Ther. 2021;26(2):205-209 10. Harbers VEM, van der Salm N, Pegge SAH, van der Vleuten CJM, Verhoeven BH, Vrancken SLAG, Schultze Kool LJ, Fuijkschot J, Te Loo DMMWM. Effective low-dose sirolimus regimen for kaposiform haemangioendothelioma with Kasabach-Merritt phenomenon in young infants. Br J Clin Pharmacol. 2022 Jun;88(6):2769-2781. 11. Czechowicz JA, Long-Boyle JR, Rosbe KW, Mathes EF, Frieden IJ, Shimano KA. Sirolimus for management of complex vascular anomalies - A proposed dosing regimen for very young infants. Int J Pediatr Otorhinolaryngol. 2018 Feb;105:48-51. 12. Cabrera TB, Speer AL, Greives MR, Goff DA, Menon NM, Reynolds EW. Sirolimus for Kaposiform Hemangioendothelioma and Kasabach-Merritt Phenomenon in a Neonate. AJP Rep. 2020 Oct;10(4):e390-e394. 13. Serio J, Gattoline S, Collier H, Bustin A. Evaluation of Sirolimus Dosing in Neonates and Infants With Lymphatic Disorders: A Case Series. J Pediatr Pharmacol Ther. 2022;27(5):447-451. 14. Triana P, Miguel M, Díaz M, Cabrera M, López Gutiérrez JC. Oral Sirolimus: An Option in the Management of Neonates with Life-Threatening Upper Airway Lymphatic Malformations. Lymphat Res Biol. 2019 Oct;17(5):504-511. 15. Laforgia N, Schettini F, De Mattia D, Martinelli D, Ladisa G, Favia V. Lymphatic Malformation in Newborns as the First Sign of Diffuse Lymphangiomatosis: Successful Treatment with Sirolimus. Neonatology. 2016;109(1):52-5. 16. Kim D, Benjamin L, Wysong A, Hovsepian D, Teng J. Treatment of complex periorbital venolymphatic malformation in a neonate with a combination therapy of sirolimus and prednisolone. Dermatol Ther. 2015 Jul-Aug;28(4):218-21. 17. Weiland MD, Bonello K, Hill KD. Rapid regression of large cardiac rhabdomyomas in neonates after sirolimus therapy. Cardiol Young. 2018 Mar;28(3):485-489. 18. Lawley C, Popat H, Wong M, Badawi N, Ayer J. A Dramatic Response to Sirolimus Therapy in a Premature Infant With Massive Cardiac Rhabdomyoma. JACC Case Rep. 2019 Oct 16;1(3):327-331. 19. Lee SJ, Song ES, Cho HJ, Choi YY, Ma JS, Cho YK. Rapid Regression of Obstructive Cardiac Rhabdomyoma in a Preterm Neonate after Sirolimus Therapy. Biomed Hub. 2017 Mar 21;2(1):1-6. 20. Breathnach C, Pears J, Franklin O, Webb D, McMahon CJ. Rapid regression of left ventricular outflow tract rhabdomyoma after sirolimus therapy. Pediatrics. 2014 Oct;134(4):e1199-202.

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VERSION/NUMBER	DATE
Original 1.0	20/06/2024
Version 1.0 (minor errata)	26/06/2024
REVIEW	20/06/2029

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Citation for the current version

Chan KJ, Bolisetty S, Mehta B, Wong M, Jackson M, Azeem MI, O-Grady R, Emerson-Parker B, Gengaroli R, Phad N, Chen C, Tran T, Halena S, Brew S, Srnic N, Malloy B, Hassall S, Houghton K, Barzegar R, Jenkins M, Adams S, Kluckow M, Allegaert K, Callander I. Sirolimus. Consensus formulary by the Australasian Neonatal Medicines Formulary group. Version 1, dated 20 June 2024. www.anmfonline.org