NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT

Shared care guidelines for use of Sirolimus for adult solid organ transplant patients
Monitoring level Amber 1 - perform higher level of monitoring e.g. 6 monthly review

Generic and Proprietary/Brand Name

Sirolimus / Rapamune®

Indications for shared care

- Post adult solid organ transplant.
- Shared-care will only be considered appropriate at least three months post-transplant and only when the immunosuppression regimen is stable.

Specialist Prescribing and Monitoring Responsibilities – summary. Full details in main body of document	GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities – summary. Full details in main body of document

• Review patient in clinic
• Inform the patient of side effects and long term monitoring before initiating treatment.
• Prescribe sirolimus for at least three months until the immunosuppression regimen is stable, co-morbid conditions are being treated and there is no longer a need for the patients to be seen as frequently in clinic.
• Inform the GP when sirolimus is initiated. When the patient is near completing a satisfactory initiation period, the physician will write to the GP to request they take over prescribing.
• Inform the patient/carers of the arrangements being made to share care with their GP, including information on who will be monitoring each aspect of therapy.
• Inform the GP of the results taken at each clinic visit. Any action required will be taken by the physician and information on any changes to medication will be given in the accompanying letter.
• Initial monitoring and at each clinic appointment, the following tests will be taken. Frequency of which is determined by clinical need:
  ○ Urea & electrolytes (inc. calcium & phosphate)
  ○ Liver function tests
  ○ Mid-stream urine (for Culture & Sensitivities)
  ○ Blood pressure
  ○ Full blood count
  ○ Lipid screening
	• Prescribe sirolimus once the patient has been stabilised on therapy and side effects have been excluded as far as possible by the hospital
	• If the GP has concerns over the prescribing of sirolimus; they will contact the physician as soon as possible.
	• Avoid drug interactions
	• Avoid live vaccines
	• Identify adverse effects and treat or report to physician where appropriate
	• If a patient presents with a likely infection, an urgent FBC and urea & electrolytes should be taken
	• Alert specialist to any identified non-compliance with immunosuppressants
	• Carry out tests as requested in writing by specialist

Patient Information

When using the oral solution mix the prescribed dose with at least 60 ml of water or orange juice in a glass or plastic container immediately before taking. Refill the container with at least 120 ml and drink immediately (to ensure total dose). Do not mix with any other liquids.

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Specialist Contact Details

- Dr. Mark Andrews Consultant Nephrologist, NNUH via secretary on 01603 286659
- Dr. Mahzuz Karim Consultant Nephrologist, NNUH via secretary on 01603 288930
- Langley Ward, NNUH on 01603 289974

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.
- **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Sirolimus is a non-calcineurin inhibiting immunosuppressant.

Licensed use and agreed local off-label use

Sirolimus is licensed for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk who have received a transplant. It is recommended that sirolimus is used initially in combination with ciclosporin and corticosteroids for 2–3 months. The marketing authorisation states that sirolimus may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued.

Criteria for Patient Selection

For adult patients who have undergone a transplant.

Sirolimus is recommended as an option as part of an immunosuppressive regimen in cases of proven intolerance to calcineurin inhibitors (e.g. ciclosporin or tacrolimus) necessitating complete withdrawal of these treatments. The intolerance might, most commonly, be due to acute or chronic nephrotoxicity.

Latest NICE guidance https://www.nice.org.uk/guidance/ta481states the circumstances under which sirolimus may be used under 3.21

Form and strength of preparation

500 microgram tablets,1 mg coated tablets, 2 mg coated tablets and 1mg/ml oral solution.
(NB The BNF states that the 500 microgram tablet is not bioequivalent to the 1 mg and 2 mg tablets. Multiples of 500 microgram tablets should not be used as a substitute for other tablet strengths)

Side Effects and Management

Link to BNF

Link to SPC

Drug Interactions

Link to BNF

Link to SPC

Sirolimus is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp) located in the small intestine. Therefore absorption and the subsequent elimination of sirolimus may be influenced by substances that affect these proteins.

Common drugs which may increase sirolimus levels:

Amiodarone / Dronedarone	Mirabegron	Live vaccines – increased risk of generalised infection
Ciclosporin – separate administration by 4 hours	Itraconazole / Posaconazole	Ketoconazole
Fluconazole	Diltiazem	Verapamil
Nicardipine	Cisapride	Clarithromycin
Metoclopramide	Erythromycin	Bromocriptine
Trolandeomycin	Cimetidine	Danazol
Protease inhibitors	Doxycycline	Voriconazole

Drugs which may decrease sirolimus levels:

Rifamipicin	Rifabutin	Phenobarbitone / Phenobarbital
Carbamazepine	St. John's Wort	Primidone
Phenytoin	Bosentan	

Grapefruit juice affects cytochrome P450 metabolism of sirolimus and should therefore be avoided.

Cautions and Contraindications

Link to BNF

Link to SPC

- Hypersensitivity to the sirolimus or to any of the excipients.
- Pregnancy unless clearly necessary. Effective contraception must be used during therapy and for 12 weeks after it has been stopped.
- Breast feeding should be discontinued during therapy.
- Afro-Caribbean patients may require higher doses.
- Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression.
- Exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
- Sirolimus is associated with increased serum cholesterol and triglycerides that may require treatment such as diet, exercise, and lipid-lowering agents.

Initiation of therapy and ongoing dose regimen

Consultant at the Norfolk and Norwich University Hospital or Addenbrooke's Hospital.

The starting dose is 4mg once a day.

Doses are individualized to achieve a whole blood trough level of 4 to 20nanogram/ml depending upon time post-transplant and concurrent immunosuppression.

Administration Information

Sirolimus is usually administered on a once daily basis.
It is important for patients to be instructed to take sirolimus on an empty stomach (one hour before or 2-3 hours after a meal to ensure consistent absorption).
It should also be taken 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

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

Long-term therapy

Baseline assessment and ongoing monitoring – by Specialist

Initial monitoring:

- Urea & electrolytes (inc. calcium & phosphate)
- Liver function tests
- Mid-stream urine (for Culture & Sensitivities)
- Blood pressure
- Full blood count
- Lipid screening

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Ongoing specialist monitoring:

At each clinic appointment the following tests will be taken, the frequency of which is determined by clinical need:

- Urea & electrolytes (inc. calcium & phosphate)
- Liver function tests
- Mid-stream urine (for Culture & Sensitivities)
- Blood pressure
- Full blood count
- Lipid screening

Evaluate any adverse events reported by the GP.

Interim tests may be required between clinic visits. If this is the case the specialist will write to the GP stating which test is to be taken and at what time. The specialist will provide the patient directly with an ICE form to receive phlebotomy from their nearest service.

GP / Community Team or other Primary Care monitoring responsibilities

- Identify adverse effects and treat or report to physician where appropriate
- If a patient presents with a likely infection, an urgent FBC and urea & electrolytes should be taken
- Alert specialist to any identified non-compliance with immunosuppressants
- Carry out tests as requested in writing by specialist

Consultant / Specialist prescribing responsibilities

- Review patient in clinic
- Inform the patient of side effects and long term monitoring before initiating treatment.
- Prescribe sirolimus for at least three months until the immunosuppression regimen is stable, co-morbid conditions are being treated and there is no longer a need for the patients to be seen as frequently in clinic.
- Inform the GP when sirolimus is initiated. When the patient is near completing a satisfactory initiation period, the physician will write to the GP to request they take over prescribing.
- Inform the patient/carers of the arrangements being made to share care with their GP, including information on who will be monitoring each aspect of therapy.

- Inform the GP of the results taken at each clinic visit. Any action required will be taken by the physician and information on any changes to medication will be given in the accompanying letter.

GP prescribing responsibilities

- Prescribe sirolimus once the patient has been stabilised on therapy and side effects have been excluded as far as possible by the hospital
- If the GP has concerns over the prescribing of sirolimus; they will contact the physician as soon as possible.
- Avoid drug interactions
- Avoid live vaccines

It is vital that doses are not changed without first consulting the physician.

Indications for referral back to Specialist

- Neutropenia (white cell count <4 * 10^9/L, neutrophils <1.3 * 10^9/L
- Significant decline in renal function
- Arthralgia
- Interstitial lung disease
- Planned major surgery where the physician will usually consider switching to another regimen for the period around the surgery.
- Mouth ulceration
- Concerns by GP or patient

Author(s) and Organisation	Dr Mark Andrews, Consultant Nephrologist, NNUH
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Document history:

Version	Date	Author / Editor	Status	Comment
1.	Sept 2007	Dr Mark Andrews, Consultant in Renal Medicine, Hannah Waller, Specialist Clinical Pharmacist Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Due for review Sept 2009

2.	Nov 2009	Dr Mark Andrews, Consultant in Renal Medicine, Claire O'Dwyer, Specialist Clinical Pharmacist Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Due for review Nov 2011
3.	Sept 2012	Dr Mark Andrews, Consultant in Renal Medicine, Claire O'Dwyer, Specialist Clinical Pharmacist Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Initial dose changed from 6mg loading dose followed by 2mg once daily, to 4mg once daily. Approved by the TAG on 6th September 2012.
4.	Oct 2014	Dr Mark Andrews, Consultant in Renal Medicine / Fiona Marshall TAG Lead Pharmacist, NEL CSU Anglia	Superseded	Updated into current TAG template format. Clinical content reviewed by the NNUH. Entry regarding timetable for repatriation of prescribing responsibility added to Additional information. **November 2014:** The TAG recommended adding under the specialist monitoring section "The specialist will provide the patient directly with an ICE form to receive phlebotomy from their nearest service".
5.	May 2016	As for 4.	Superseded	Continued need reviewed by the TAG – repatriation not complete and homecare services not yet established. Use to be extended by another year – revisit May 2017. 500mcg strength tablets added to the formulations list with related BNF warning that should not be used as a substitute for the 1mg or 2mg tablets due to not being bioequivalent to those strengths. Reference to Leeds SCG updated. Reference to Addenbrooke's SCG deleted since no longer accessible on-line. Hyperlinks to manufacturer's SPC and PILs added.
6.	Nov 2017	As for 4.	Current	Continued need reviewed by the TAG – repatriation not complete.

				Use to be extended by another 6 months – revisit May 2018. Link to current NICE guidance updated. Interactions section updated in line with BNF.
7.0	Aug 2021	Jen Carroll, TAG Lead Technician	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
8.0	Feb 2024	Jen Carroll, TAG Lead Technician	FINAL	Content not reviewed. 'Renal' removed as now covers all solid organ transplants Existing SCA transferred to new template For TAG approval