Shared Care Guideline

Sirolimus (Rapamune®) for Maintenance of Immunosuppression after Kidney Transplantation in Adults

Executive Summary

- Sirolimus (Rapamune) is licensed for the maintenance of immunosuppression following transplantation in adults at low to moderate immunological risk receiving a renal transplant.
- Patients will have been stabilised on post transplant immunosuppression by the transplant centre.
- Patients will be on a maintenance dose of sirolimus and other specialist medicines before shared care with primary care is requested.
- GPs are asked to prescribe sirolimus (Rapamune®) at the dose determined by the hospital specalist
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope
This document provides information on the prescribing and monitoring of sirolimus post kidney transplant.

2. Aim
The aim is to provide information and guidance on sirolimus post renal transplant.

3. Introduction
Sirolimus is licensed for the maintenance of immunosuppression following transplantation in adults at low to moderate immunological risk receiving a renal transplant. It is recommended to be used initially with ciclosporin and corticosteroids for 2 to 3 months, and may be continued only if ciclosporin can be progressively discontinued.
Sirolimus inhibits T-cell activation induced by most stimuli. Sirolimus binds to the specific cytosolic protein FKPB-12 and the FKPB-12-sirolimus complex inhibits the activation of the mammalian Target of Rapamycin (mTOR). 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.
Patients will have been stabilised on post transplant immunosuppression by the transplant centre. Patients will be on a maintenance dose of sirolimus and other specialist medicines before shared care with primary care is requested.

4. Abbreviations
- mTOR - mammalian Target of Rapamycin
- SmPC – summary of product characteristics

5. Dose and Administration
- The recommended dose is 6 mg initially, followed by 2 mg per day for 2 to 3 months, then adjusted to obtain blood trough levels of 4 to 12 nanograms/ml.
- After discontinuation of ciclosporin the maintenance dose will be adjusted to achieve whole blood trough levels of 8 to 12 nanograms/ml.
- To minimise bioavailability problems the dose should be taken consistently either with or without food.
- Sirolimus is available as 0.5mg, 1mg and 2mg tablets and as 1mg/ml oral solution.
- Multiples of 0.5 mg tablets should not be used as a substitute for the 1 mg tablet or for other strengths.

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/product/1368/smpc

6. Adverse Effects

Very common (≥ 1 in 10)
- Pneumonia; fungal infection; viral infection; bacterial infection; herpes simplex infection; urinary tract infection
- Thrombocytopaenia; anaemia; leucopenia

- Hypokalaemia; hypophosphataemia;hyperlipidaemia (including hypercholesterolaemia); hyperglycaemia; hypertriglyceridaemia
- Diabetes mellitus
- Headache
- Tachycardia
- Hypertension; lymphocele
- Abdominal pain; diarrhoea; constipation; nausea
- Rash; acne
- Arthralgia
- Proteinuria
- Menstrual disorder (including amenorrhoea and menorrhagia)
- Oedema; oedema peripheral; pyrexia; pain; Iimpaired healing
- Blood lactate dehydrogenase increased; blood creatinine increased; liver function test abnormal (including alanine aminotransferase increased and aspartate amino-transferase increased)

Common (≥ 1 in 100 and < 1 in 10)

- Sepsis; pyelonephritis; cytomegalovirus infection; herpes zoster infection caused by the varicella zoster virus
- Non-melanoma skin cancer
- Haemolytic uraemic syndrome; neutropaenia
- Hypersensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction)
- Pericardial effusion
- Venous thrombosis (including deep vein thrombosis)
- Pulmonary embolism; pneumonitis; pleural effusion; epistaxis
- Pancreatitis; stomatitis; ascites
- Osteonecrosis
- Ovarian cyst

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Clostridium difficile colitis; mycobacterial infection (including tuberculosis); Epstein-Barr virus infection
- Lymphoma; malignant melanoma; post-transplant lymphoproliferative disorder
- Pancytopaenia; thrombotic thrombo-cytopaenic purpura
- Lymphoedema
- Pulmonary haemorrhage
- Hepatic failure
- Dermatitis exfoliative
- Nephrotic syndrome; focal segmental glomerulosclerosi

Rare (≥ 1 in 10000 and < 1 in 1000)

- Alveolar proteinosis
- Hypersensitivity vasculitis

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/product/1368/smpc

7. Cautions

- Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis, have been associated with the administration of sirolimus
- Patients should be monitored for elevated lipids. Patients administered an HMG-CoA reductase inhibitor or fibrate should be monitored for rhabdomyolosis and other adverse effects as per the SmPCs for those products.
- Co-administration of sirolimus with strong inhibitors or inducers of CYP3A4 isozyme – see interactions below.
- Immunosuppressants may affect response to vaccination. During treatment with sirolimus vaccination may be less effective. The use of live vaccines should be avoided during treatment with sirolimus.
- Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression.
- Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections, and sepsis.
- In hepatically impaired patients, it is recommended that sirolimus whole blood trough levels be closely monitored.
- The use of Rapamune in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment.

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/product/1368/smpc

8. Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Sirolimus oral solution contains soya oil. Patients allergic to peanut or soya must not take this medicine.

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/product/1368/smpc

9. Interactions

- Grapefruit juice increases levels of sirolimus and should not be taken.
- Rifampicin and Rifabutin are CYP3A4 isozyme inducers – co-administration with sirolimus is not recommended as sirolimus levels will be decreased.
- Voriconazole, ketoconazole are CYP3A4 isozyme inhibitors – co-administration with sirolimus is not recommended.
- If diltiazem (a CYP3A4 inhibitor) is administered sirolimus levels should be monitored and dose adjustment may be necessary.
- If Verapamil (a CYP3A4 inhibitor) is co-administered sirolimus levels should be monitored and appropriate dose reductions of both products considered.
- Where there is co-administration with erythromycin (CYP3A4 inhbitor) sirolimus levels should be monitored and appropriate dose reductions of both medicinal products should be considered.

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/product/1368/smpc

10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

- Monitoring is the responsibility of secondary care, although the bloods may be taken in primary care. Sirolimus trough levels, full blood counts, urea and electrolytes and liver function tests every six months, and lipid profiles every 12 months
- All blood results will be copied to the prescribing GP surgery.
- The hospital specialist will follow up and action all monitoring blood results, adjust the Sirolimus dose if needed, arrange for repeat trough levels after any dose adjustments, and communicate any dose changes with the patient and the prescribing GP surgery.
- The hospital specialist should be contacted if the patient experiences any unusual or serious adverse effect.

11. Shared Care Responsibilities

a. Hospital specialist:

- Send a letter to the GP requesting shared care for the patient.
- Clearly highlight in any correspondence with the GP that Sirolimus should prescribed
- by brand name (Rapamune®).
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- To provide any advice to the patient/carer when requested.

b. General Practitioner:

- Agreement to shared care guideline by the GP.
- Ensure timely prescribing of an adequate amount of immunosuppressive drugs.
- Sirolimus should be prescribed by brand name (Rapamune®).
- Monitor patient's overall health and well-being.
- Report any adverse events to the hospital specialist, where appropriate.
- Inform the hospital if any new medication that may interfere with Sirolimus is to be commenced.

c. Patient or parent/carer:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.
- Keep exposure to sunlight and ultraviolet light to a minimum by wearing protective clothing and using a sunscreen with high sun protection factor to minimise risk of skin cancer.
- Report any sign of infection (raised temperature, cough), unexpected bruising or bleeding to your doctor.

12. Contact numbers for advice and support

North West Anglia Foundation Trust		
Specialist	**Post**	**Telephone**
Frieder Kleemann	Nephrologist	07788 301 219
Renal on-call SpR Leicester		Via UHL switchboard: 0300

General Hospital		303 1573

13. Equality and Diversity Statement

This document complies with the North West Anglia Foundation Trust's service Equality and Diversity statement.

14. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics https://www.medicines.org.uk/emc/product/1368/smpc

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