NHS LINCOLNSHIRE in association with
UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE:
Sirolimus for Maintenance of Immunosuppression after Kidney Transplantation in Adults

General Principles

Shared Care Responsibilities:
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (*BNF* 70, September - March 2016, pg.4)

Aims:
(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.

(2) Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.

(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.

(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between the Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies

Further copies of any guidelines in this series are available from members of the Arden and GEM commissioning Support Unit – Lincolnshire Prescribing & Medicines Optimisation Team.

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Drug Details

Approved Name: Sirolimus

Brand Name: Rapamune®

Form and Strength: Tablets 500 micrograms,1mg and 2mg, oral solution 1mg per ml.

Specialist Responsibilities

The specialist secondary/tertiary care service will:

All patients eligible for treatment under this protocol will have received their renal transplant at least one year ago and will now be transferred to the care of the Lincoln based renal services.

1. Send a letter to the GP notifying them of the changes to the ongoing care of the patient and asking them if they are willing to accept share care, and confirm that they will continue to provide regular prescriptions for sirolimus.
2. Ensure that the patient receives supplies of sirolimus until the GP formally agrees to share care, except in those circumstances where the patient already receives these medications from the GP under a prior arrangement
3. Measure biochemistry including sirolimus levels, U&Es, liver function tests and full blood counts in line with local and national guidelines/protocols.
4. Titrate the dose of sirolimus as necessary to the optimum level according to blood results and local/national guidelines.
5. Advise the GP when the dose should be changed.
6. Provide patient with treatment information leaflet.
7. Communicate promptly any changes in monitoring and modification of sirolimus dose to the GP.
8. Communicate promptly any changes in test results to the GP.
9. Periodically (at six-monthly intervals in clinic) review the patient's clinical condition.
10. Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
11. Follow up any adverse drug reactions reported by the GP and report back to the GP.
12. Advise the GP on related issues such as drug interactions.
13. Respond to issues raised by the GP after the care of the patient has been transferred.

GP Responsibilities

The GP will:

1. Notify the consultant in writing, within two weeks, if they agree to share care.
2. Provide repeat prescriptions after achievement of a stable dose regime according to recommendations by the Nephrology department, Lincoln County Hospital.
3. Monitor the patients overall health and wellbeing.
4. Ensure advice is sought from the secondary care clinician if there is any significant change in the patient's physical health status.
5. Monitor the patient for adverse drug reactions and abnormalities and remain vigilant to the risk of potential drug interaction, and raise these issues with the secondary care clinician if necessary.
6. Carry out any investigations that are communicated and deemed appropriate.
7. Change the dose or stop treatment in line with instructions from the secondary care clinician.
8. Consult promptly with the specialist when test results are abnormal or when patient defaults from blood test appointments undertaken by primary care.

Referral Criteria

1. Patients will have been stabilized on their immunosuppressants, and other specialist medications.
2. Patients will have received their renal transplant at least 12 months ago and their ongoing supervision and care will have been transferred to the Lincoln based renal services.
3. The specialist will have carried out an assessment of efficacy.

Licensed Indications

Sirolimus is licensed for the maintenance of immunosuppression following kidney transplantation in adults.

Current NICE guidance states sirolimus should only be used in renal transplant patients if the patient is intolerant to a calcineurin inhibitor.

Recommended Dosage and Administration

Sirolimus (Rapamune®)
Starting dose: Dose is according to levels, usually 2-3mg once daily.
Maintenance dose: Sirolimus level aimed for is 10 nanograms/ml at 1 year post kidney transplant. Drug levels will be measured and dose alterations will be carried out by secondary care.
To minimise variability in bioavailability from doses taken, Rapumune should consistently be taken either with or without food.

Background Pharmacology

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.

Preparations Available

0.5mg,1mg, 2mg capsules of sirolimus and oral solution 1mg/ml (Rapamune®)
The 0.5mg tablet is not bio-equivalent to the 1mg or 2mg tablets. Multiples of 0.5mg tablets should not be used as a substitute for other tablet strengths.

Adverse Effects

Very common and common adverse effects are: Abdominal pain, acne,anaemia, arthralgia, ascites, constipation, diarrhoea, epistaxis, haemolytic uremic syndrome, headache, hypercholesterolaemia, hyperglycaemia, hypertension, hypertriglyceridaemia, hypokalaemia, hyperphosphataemia, impaired healing, leucopenia, lymphocele, nausea, neutropenia, oedema, osteonecrosis, pleural effusion, pneumonitis, proteinuria, pyrexia, rash, stomatitis, tachycardia, thrombocytopenia, thrombotic thrombocytopenia purpura, venous thromboembolism.
Uncommon : Nephrotic syndrome, pancreatitis, pancytopenia, pericardial effusion, pulmonary embolism, pulmonary haemorrhage.
Rare: Alveolar proteinosis, anaphylactic reactions,angioedema, exfoliative dermatitis, hepatic necrosis, hypersensitivity reactions, hypersensitivity vasculitis, interstitial l lung disease, lymphoedema.

Frequency not known: Focal segment glomerulosclerosis, reversible impairment of male fertility.
For full details of adverse effects please refer to current edition of BNF or the products summary of product characteristics (SPC)

Drug Interactions

a) Antibacterials - levels of sirolimus increased by: clarithromycin, telithromycin, – BNF advises avoid concomitant use.
b) Levels of both sirolimus and erythromycin are increased when both drugs used together
c) Levels of sirolimus decreased by: rifabutin, rifampicin. BNF advises avoid concomitant use.
d) Levels of sirolimus increased by itraconazole, ketoconazole, voriconazole – BNF advises avoid concomitant use.
e) Levels also increased by micafungin, miconazole, and possibly by fluconazole and posaconazole.
f) Levels of sirolimus possibly increased by atazanavir, lopinavir, and levels of both sirolimus and telaprevir are increased if used concomitantly. Plasma levels increased by boceprevir leading to increased risk of toxicity.
g) Levels increased with grapefruit juice – avoid concomitant use.
h)Calcium channel blocker - Levels of sirolimus increased with diltiazem. Plasma concentration possibly increased by nicardipine. Plasma concentrations of both drugs increased when sirolimus given with verapamil.
i) Levels of sirolimus increased by ciclosporin. Appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels. Caution should be exercised when co-administering other agents that are known to have a deleterious effect on renal function.
j) The manufacturer of dronedarone advises caution if used with sirolimus
k) cytotoxics – manufacturer advises caution if sirolimus used with crizotinib.

Precautions and Contraindications

Precautions

Renal function

Kidney function needs careful monitoring if administering in combination with ciclosporin.
Sirolimus may delay recovery of renal function in patients with delayed graft function.

Afro-Caribbean patients

Afro-Caribbean patients may require higher doses need to monitor whole blood sirolimus trough concentration.

Hepatic impairment

Hepatic impairment - monitor whole blood sirolimus level closely, clearance is reduced in mild to moderate impairment, in severe impairment decrease dose by 50% and monitor whole blood sirolimus trough concentration every 5-7 days until 3 consecutive measurements have shown stable blood sirolimus concentration.

Hyperlipidaemia

Reports of increased serum cholesterol and triglycerides that may require treatment. Patients administered Rapamune should be monitored for hyperlipidaemia using laboratory tests and if hyperlipidaemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents should be initiated. The risk/benefit should be considered in patients with established hyperlipidaemia before initiating an immunosuppressive regimen, including Rapamune. Similarly the risk/benefit of continued Rapamune therapy should be re-evaluated in patients with severe refractory hyperlipidaemia

Infections

Increased susceptibility to urine infections – monitor urine proteins.
Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections, and sepsis.
Among these conditions are BK virus-associated nephropathy and JC virus-associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.
Cases of Pneumocystis carinii pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for Pneumocystis carinii pneumonia should be administered for the first 12 months following transplantation.
Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

Risk of malignancy

Increased susceptibility to lymphoma and other malignancies, particularly of the skin advise patients to limit exposure to UV light.
Rapamune has not been adequately studied in patients at high immunological risk, therefore use is not recommended in this group of patients.

Delayed healing

There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele and wound dehiscence. Patients with a body mass index (BMI) greater than 30 kg/m2 may be at increased risk of abnormal wound healing based on data from the medical literature.

Fluid accumalation

There have also been reports of fluid accumulation, including peripheral oedema, lymphoedema, pleural effusion and pericardial effusions (including haemodynamically significant effusions in children and adults), in patients receiving Rapamune.

Contraindications

Pregnancy, Toxicity reported in animal studies. Avoid use unless essential.
Effective contraception should be used during treatment and for 12 weeks after stopping.
Breast feeding do not use, advise to discontinue breast feeding.
Hypersensitivity to sirolimus or any of the excipients
Rapamune oral solution contains soya oil, therefore patients allergic to peanut or soya should not take this product.

Sirolimus tablets contain sucrose and lactose. Use needs to be avoided in patients with rare hereditary problems of fructose intolerance or galactose intolerance,

Monitoring

Sirolimus Levels, Full blood counts, U and Es and Liver Function Tests every 6 months or more frequently. Monitoring is the responsibility of the secondary care service although some testing may be devolved to the primary care setting.

Additional monitoring of drug levels is required in hepatic impairment and during treatment with potent inducers or inhibitors of hepatic metabolism, and after discontinuing them.

Treatment should be reviewed and advice from the supervising specialist sought if:

-there is deterioration in the clinical condition and/or the patient experiences major side-effects.
-serum creatinine levels rise by >20% in 3 months.

Indication of Likely Cost of Therapy in Primary Care

January 2016

Sirolimus (Rapamune®) 0.5mg	£69.00 for 30 tablets
Sirolimus (Rapamune®) 1mg	£86.49 for 30 tablets
Sirolimus (Rapamune®) 2mg	£172.98 for 30 tablets
Sirolimus (Rapamune®) liquid (1mg in 1 ml)	£162.41 for 60ml

Information Given to the Patient

Patient information leaflet available with each container of sirolimus (Rapamune®)

Contact Details

Lincoln Renal Unit: 01522 573961

Caroline Taylor: 01522 573598
Renal Pharmacist
County Hospital

References

1. BNF 70 September 2015 - March 2016.
2. SPC for Rapamune® , Pfizer Limited eMC updated 27.10.2015 accessed from EMC website 27th January 2016.
3. Drug Tariff January 2016
4. MIMS September 2015

Authors:
Dr Matt Williams- Consultant Nephrologist, United Lincolnshire Hospital Trust
Dr Rebecca Hardy- Consultant Nephrologist, United Lincolnshire Hospital Trust
Caroline Taylor -Renal Pharmacist, United Lincolnshire Hospital Trust
Cathy Johnson -Interface Prescribing Manager, Lincolnshire PCT
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