Basingstoke,Winchester and Southampton District Prescribing Committee

Shared Care Guideline: **Sirolimus**

Name of patient treated under this guideline:

This shared care guideline has been produced to support the seamless transfer of prescribing and patient monitoring from secondary to primary care, and provides an information resource to support clinicians providing care to the patient. It does not replace discussion about sharing care on an individual patient basis.

This guideline was prepared using information available at the time of preparation, but users should always refer to the manufacturer's current edition of the Summary of Product Characteristics (SPC or "data sheet") for more details.

1.0 Status of the Drug

Sirolimus is a non-calcineurin, potent immunosuppressant that can be used in patients who are intolerant to calcineurin inhibitors (tacrolimus, ciclosporin). Sirolimus has a differing mode of action to the calcineurin inhibitors and has not been shown to have the nephrotoxic and hypertensive side effects that are associated with them.

Shared-care will only be considered once the patient has been stabilised on an immunosuppressant regimen and the patient is at least three months post transplant. In addition if the patient has any related conditions e.g. hypertension then these will be treated before shared care is requested.

Sirolimus is an "amber" drug using our local traffic light system. This means that treatment will be initiated in secondary care. When the patient is stabilised on the medication shared care arrangements can be considered. The key principle is that the GP is provided with information and given the opportunity to accept (or decline) prescribing responsibility before the transfer occurs. In accepting prescribing responsibility the GP also accepts responsibility for undertaking the activities outlined in this shared care guideline. Shared care arrangements should be definitive and agreed between the consultant, GP and patient.

2.0 Licensed Indications and Dose

At present Sirolimus is only licensed for the prevention of rejection in renal transplant patients. At Southampton University Hospitals NHS Trust we follow guidance from the Addenbrookes transplant team and use sirolimus off-license for the prevention of rejection in liver transplant patients. It is for this off-license use that these guidelines have been developed.

Sirolimus should not be employed immediately post transplant due to the risk of impaired wound healing. The SPC recommends initial therapy at 2-3 months post renal transplant.

A loading dose is occasionally required but will be prescribed by the hospital if needed. The usual starting dose of sirolimus is 2mg once a day (taken in the morning). It is important that the dose is taken once a day at the same time of day and at the same time in relation to food. This will ensure that drug absorption is reliable and unaffected by the presence of food in the gastrointestinal tract; to enable accurate interpretation of blood levels

All monitoring of sirolimus blood concentrations will be done in secondary care, when the patient attends a hospital clinic. On the morning of their visit they will be asked to delay their dose until after the blood test so that levels are representative of a trough. The dose of sirolimus will be adjusted by the consultant to achieve a level of 4-12nanograms/ml. The level being aimed for depends on when the transplant took place and other co-prescribed immunosuppressants. Clinic appointments and blood level checking are planned for every 3 months for the first two years post transplant and then on a 6 monthly basis thereafter.

Sirolimus is available as 1mg tablets, 2mg tablets and a 1mg/ml solution, in a 60ml bottle. Sirolimus liquid must be kept refrigerated. Sirolimus tablets should be stored at room temperature. The oral solution and oral tablets can be considered to be bioequivalent and as such doses are interchangeable.

3.0 Referral Criteria

Sirolimus will be considered as an immunosuppressant for adult liver transplant patients who are intolerant of sirolimus or who have had a second biopsy proven rejection episode

4.0 Patient Selection

Sirolimus will be considered as an immunosuppressant for adult liver transplant patients who have developed renal impairment or hypertension whilst being treated with calcineurin inhibitors. It may also be used for patients whose transplant was due to Hepatitis C virus or Hepatocellular carcinoma.

5.0 Safety Issues

5.1 Contra-indications (see BNF or SPC)

- Hypersensitivity to the active substance or to any of the excipients in the formulation.

5.2 Cautions (see BNF or SPC)

- Patients treated with sirolimus will be immunocompromised and have an increased susceptibility to infection (including bacterial, protozoal, fungal and viral).
- Patients treated with sirolimus should avoid the use of "live" vaccines; the response to vaccinations may be altered in immunocompromised patients. Specialist advice should be sought if wishing to vaccinate this group of patients.
- There is an increased risk of developing lymphomas and other malignancies (especially of the skin) whilst receiving immunosuppressive therapy.
- Sirolimus tablets contain sucrose and lactose. If a patient has a history of sucrase insufficiency, isomaltase insufficiency, fructose intolerance, glucose malabsorption, galactose intolerance, or Lapp lactase deficiency, a careful risk/benefit assessment should be performed before deciding to prescribe sirolimus tablets.
- Sirolimus should not be used during pregnancy and effective contraception must be used throughout the treatment and for 12 weeks after treatment has finished.
- Sirolimus should not be taken whilst breastfeeding. It is not known if sirolimus is excreted into breast-milk but there is a potential for adverse reactions in a breastfed infant.

5.3 Common Side Effects (See BNF or SPC)

Sirolimus is a "black triangle" medication, meaning that the MHRA monitors its use intensively. All suspected adverse drug reactions should be reported through the yellow card scheme (see BNF for more details).

Any adverse effects detected should be reported directly to the Consultant - it is vital that drug doses are not changed without consultation. See the manufacturer's SPC & BNF for full details.

Very Common (≥ 1/10**)**: Abdominal pain, Acne, Anaemia, Arthralgia, Constipation, Diarrhoea, Headache, Hypercholesterolemia, Hyperglycaemia, Hypertension, Hypertriglyceridemia, Hypokalaemia, Hypophosphataemia, Increased creatinine, Increased lactic dehydrogenase (LDH), Lymphocele, Nausea, Pain, Peripheral oedema, Pyrexia, Thrombocytopenia, Urinary tract infection.

Common (≥ 1/100, <1/10): Abnormal healing, Abnormal LFTs (Increased ALT,AST), Bone necrosis, Epistaxis, Fungal, viral, and bacterial infections, Herpes simplex, Leucopenia, Neutropenia, Oedema, Pleural Effusion, Pneumonia, Pneumonitis, Proteinuria, Pyelonephritis, Rash, Sepsis, Skin cancer, Stomatitis, Tachycardia, Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, Venous thromboembolism

5.4 Drug Interactions (see BNF or SPC)

Sirolimus interacts with many drugs that share the same metabolic pathway with it. The primary route of metabolism is via the CYP3A4 isoenzyme of the cytochrome P450 group in the intestinal wall and liver. Inhibitors of CYP3A4 may increase levels of sirolimus by reducing its metabolism and vice versa. Care needs to be taken if starting a patient on a drug that is metabolised by CYP3A4 and initiation should be discussed with a hospital specialist.

The following is not an exhaustive list; for further information on interactions with sirolimus please consult the SPC, BNF or contact the SUHT medicines information department.

Table 1: Drugs That Have Documented Interactions with Sirolimus

Interacting Drug	Effect on Sirolimus Levels
Ciclosporin	Increased
Ketoconazole, Clotrimazole, Fluconazole	Increased
Voriconazole, Miconazole	Increased
Diltiazem, Verapamil, Nicardipine	Increased
Erythromycin, Clarithromycin	Increased
Bromocriptine	Increased
Cimetidine	Increased
Protease Inhibitors	Increased
Danazol	Increased
Atazanavir, lopinavir	Increased
St Johns Wort	Decreased
Carbamazepine, phenobarbitone, phenytoin	Decreased
Rifampicin, Rifabutin	Decreased

Patients should be advised to not drink grapefruit juice as this has been shown to increase sirolimus levels. There may be a similar interaction with cranberry juice so patients should avoid this as well.

5.5 Pre-treatment Assessment

- Liver function and clotting
- Renal Function
- Full blood count
- Lipid profile

5.6 Routine Safety Monitoring

- Sirolimus blood levels will be monitored by the hospital clinic:
    - Weekly for the first month post transplant
    - Then monthly for the next 2 months
    - Then every 3 months until the patient is two years post transplant
    - And then every 6 months thereafter.

  The consultant will review the dose of sirolimus prescribed, based on the blood level obtained to ensure that the levels are therapeutic and not toxic. The consultant will advise the GP in writing and inform the patient of any changes made to the sirolimus dose.
- Liver function tests & clotting, creatinine, urea &electrolytes, full blood count and lipid screening will initially be performed by the hospital. This will be taken over by the GP when they agree to shared care. These bloods will need to be checked every 1-3 months by the GP.
- If any unusual or serious adverse effect is detected by the GP or if a full blood count/liver function test/cholesterol is found to be abnormal the GP must contact the hospital specialist for further advice.

6.0 Role of Consultant

The decision to use sirolimus will be made by a specialist hepatology consultant.

1. To assess the suitability of the patient for treatment with sirolimus.
2. To discuss relevant safety issues with the patient, and to make them aware of cautions and side effects.

3. To initially prescribe and stabilise the patient on treatment. Prescribing should continue until at least 3 months post transplant.
4. To provide the patient with a current medication card for monitoring and/or to alert other clinical staff to the treatment they are receiving (or update the one they already hold).
5. To measure Sirolimus bloods levels every 1- 3 months as clinically needed for the first 2 years post transplant and then every 6 months thereafter, and advise on changes of dose in relation to blood levels.
6. To monitor liver function tests & clotting, creatinine, urea &electrolytes, full blood count and lipid screening every 1-3 months as clinically needed, whilst prescribing remains in secondary care.
7. To monitor for treatment efficacy, for side effects and the patient's general condition every 3-6 months in clinic.
8. To ask the GP in writing whether they are willing to participate in shared care, this should include a copy of the shared care guideline.
9. To evaluate and answer any adverse events or concerns reported by the GP or patient.
10. To ensure prompt communication in writing with the GP of any changes to treatment, of assessment of response and any occurrence of adverse effects.
11. To advise the patient of arrangements being made to share care with their GP, including information of who will be monitoring each aspect of therapy and what side effects and concerns to report (and to whom).
12. Inform the GP of information given to the patient and if they have been given a medication card.

7.0 Role of GP

1. To ensure all practice staff are aware of this shared care guideline.
2. To prescribe oral sirolimus maintenance treatment according to dosage instructions from the hospital consultant. This will be at least 3 months post transplant and in accordance with this shared care guideline.
3. To report any suspected adverse effects to the hospital consultant and MHRA as needed.
4. To monitor liver function tests & clotting, creatinine, urea &electrolytes, full blood count and lipid screening every 1-3 months for the first 2 years post transplant and then every 6 months thereafter, once shared care has been agreed and prescribing has been taken over.
5. To contact the consultant if there are any concerns based on blood test results for advice.
6. Encourage patients to carry an up to date medication card.
7. Check for possible drug interactions when newly prescribing or stopping concurrent medication.
8. Report to and seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment.
9. Confirm with the specialist which changes in monitoring or other parameters should trigger urgent referral back to the specialist.
10. Administer the influenza vaccine annually.

11. Role of Patient

1. To take medications as prescribed.
2. Report any adverse effects to their GP or hospital consultant whilst taking the sirolimus.
3. Ensure they have a clear understanding of their treatment and raise any outstanding queries.
4. Hold a medication record card and ensure it is updated. Alert other clinical staff to the treatment they are receiving.
5. Ensure correct administration and storage of the sirolimus
6. To attend hospital clinic and GP appointments as necessary and have blood tests at the appropriate time intervals.

7. Further Information

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Approved by Basingstoke Southampton and Winchester District Prescribing Committee (12 April 2011):
Review date: April 2014