Supplementary Material: Sirolimus / Everolimus protocol for the Treatment of Congenital Hyperinsulinism

1. Purpose

This document provides a framework for all members of trust staff involved in the clinical care of children and young people. It provides information on the management of children and young people requiring treatment with sirolimus or everolimus.

2. Sirolimus / Everolimus protocol for the Treatment of Congenital Hyperinsulinism

2.1. Background

Sirolimus is an immunosuppressive drug that inhibits the serine/threonine kinase mammalian target of rapamycin (mTOR). Inhibition of mTOR by sirolimus causes cell cycle arrest in mild to late G1 phase. These effects are responsible for repression of tumour cell growth and inhibition of T and B cell proliferation.

Sirolimus has been approved by US Food and Drug Administration (FDA) for the prophylaxis of renal transplant rejection since 1999 for patients of age 13 years and older. Sirolimus has also been used in metastatic malignant insulinomas in adults, with satisfactory control of hypoglycaemia.

Sirolimus has been used in children with Congenital Hyperinsulinism (CHI) in small observational studies and case reports recently, with the youngest patient being 7 weeks of age. The mechanism of mTOR inhibition in CHI which causes a reduction in hypoglycaemia is not clear, although downstream action on insulin receptor signalling and disconnection between amino acid and energy-sensing pathways in the pancreatic beta cells have been proposed as explanations. Long term experience of using sirolimus in children with CHI remains minimal. There are concerns regarding serious adverse events from sirolimus use including infections, pulmonary toxicity, abnormalities of lipid metabolism, liver dysfunction and renal toxicity.
**Sirolimus** is not licensed for use in CHI. It is important that sirolimus is prescribed for CHI use with due consideration and monitoring of efficacy and adverse events.

Another mTOR inhibitor is commercially available, **everolimus**. **Everolimus** has an improved oral bioavailability and pharmacokinetics, as well as a reduced immunosuppressive activity. **Everolimus** is approved by the FDA for patients with advanced renal cell carcinoma (after failure of treatment with sunitinib or sorafenib) and advanced pancreatic neuroendocrine tumors, as well as subependymal giant cell tumors and angiomyolipoma associated with tuberous sclerosis complex (adults and children >3 years of age). The therapeutic efficacy and safety of **everolimus** have been demonstrated in multicenter, international, randomized, double-blind, placebo-controlled trials. **Everolimus** is generally well tolerated, with the most frequently reported adverse events including rash, mucositis, fatigue, and headache.

The pharmacokinetics and safety of **everolimus** in children have been reported in a paediatric phase I study (with refractory solid tumors), a phase II study (in children and adults with neurofibromatosis type 2 and progressive vestibular schwannomas), and a in review where the paediatric population was concerned (in the treatment of subependymal giant cell astrocytomas, angiomyolipomas, and pulmonary and skin lesions associated with tuberous sclerosis complex).

**Everolimus** is not licensed for use in CHI and has not been tried before in CHI. Trial of treatment with everolimus should be conducted in a centre with paediatric experience of everolimus.

The case for commencing **sirolimus or everolimus** has to be made following discussion within the CHI multidisciplinary team. Trial of treatment with **sirolimus / everolimus** has to be discussed with parents/caregivers with consent obtained on currently available consent forms with a copy filed in the case notes.

### 2.2. Pharmacokinetics

- **Sirolimus**:
  - Is administered orally, absorbed rapidly with peak serum concentrations reached after 1-2 hours of administration,
- The mean elimination half-life is 62 hours,
- Attainment of steady-state concentrations: 6 days,
- The oral solution has lower bioavailability (14%) than the tablet form (27%). Bioavailability of the oral solution is further reduced after a high fat meal, hence sirolimus should be prescribed prior to a feed, not immediately after it,
- Sirolimus has a short half-life in children (mean t ½ 11.8 hours), therefore twice a day dosing may be necessary; however in adults once daily dosing is standard.

- **Everolimus:**
- Everolimus rapidly absorbed within 30 minutes to 1 hour,
- The mean elimination half-life is 28 hours,
- It has a more rapid attainment of steady-state concentrations than sirolimus: 4 days,
- Bioavailability is also reduced after a high fat meal, hence everolimus should be prescribed prior to a feed, not immediately after it (delays the median time to maximum concentration by 1.25 hours (median) and reduces the maximum serum concentration by 60%),
- Everolimus pharmacokinetics in children are comparable with those in adults.

3. **Main objective**

The goal of the sirolimus / everolimus treatment is to improve the care of severe CHI patients by improving their glycaemia and decreasing the need for invasive or burdensome treatments (Glucagon, frequent feeds, intravenous glucose, surgery of diffuse form of CHI).

4. **Practical sketch**

4.1. **Indication**

4.1.1. **Inclusion criteria**

- Children older than 2 weeks with persistent and severe CHI with or without mutations in the KATP channel genes,
- Unresponsive to large dose oral diazoxide (10-15mg/kg/day) and subcutaneous or intravenous octreotide (30-50microgram/kg/day),
- Therefore patients may require continuous glucose and/or glucagon infusion and/or frequent/continuous oral/enteral carbohydrate enriched feeds, at the time sirolimus is considered.

4.1.2. **Exclusion Criteria and Contra-indications**

**In the following circumstances the use of sirolimus is deemed inappropriate:**

- Children with suspected or confirmed focal CHI, who are candidates for surgical resection,
- Patients responding satisfactorily to diazoxide or octreotide without significant adverse events.

**Contra-indications**

- Biochemical evidence for clinically significant hepatobiliary, renal, hematologic, infectious disease as shown by:
  - ALT, AST and total bilirubin > 2.5 times the upper limit of normal
  - Serum creatinine > 2.5 times the upper limit of normal
  - Serum cholesterol levels > 5 mmol/l
  - Serum triglyceride levels > 1.5 mmol/l
  - Haemoglobin < 90 g/L
  - Neutrophil polynuclear < 1 x10⁹/L
  - Platelet count < 100 x10⁹/L
  - CRP and/or White cell count suggestive of active infection
- Evidence of active infection,
- Evidence of cardiac or respiratory failure,
- Known immune deficiency,
- Preterm baby < 37 weeks of corrected gestation,
- Treatment with other immunosuppressant,
- Treatment with any drug known to interact significantly with sirolimus,
- Hypersensitivity to soya or peanuts (oral sirolimus contains soya oil),
• Any investigational medicinal product (IMP) used within 5 half-lives of the product prior to initiation of therapy. Subjects who had participated in an investigational drug study will be eligible to participate after 5 half-lives from the last dose of the investigational agent and have recovered from acute investigational agent associated toxicity.

• **Cautions**
Live vaccines should not be administered during treatment and for 6 weeks after stopping treatment.
Sirolimus should be stopped two weeks prior to surgery.

4.2. **Investigations**

The following investigations must be carried out before commencing treatment with sirolimus:

- Weight, length, buccal exam,
- Full blood count and blood film,
- Liver function test and coagulation,
- Faecal elastase,
- Serum electrolytes,
- Renal function,
- CRP,
- Lipid profile,
- Baseline ECG,
- Thoracic X-ray,
- Thyroid function test,
- +/- TORCH screening in neonates.

4.3. **Prescription**

- Clearly record the date sirolimus / everolimus treatment is commenced,
- Start sirolimus at 0.5-1mg/m²/day in two divided doses,
- Start everolimus at 2.5 mg/m²/day in two divided doses,
• Prescribe the doses 15 minutes pre-feed/meal,
• Patient may continue on other medication to prevent hypoglycaemia, such as diazoxide, octreotide or glucagon.

4.4. Administration

• **Sirolimus (Rapamune®, Pfizer)** will be given as syrup in a concentration of 1mg/mL.
The oral solution is viscous and can be irritant to the upper gastrointestinal tract, resulting in ulceration. It should therefore be diluted as much as is reasonable to expect the child to drink.
• **Everolimus (Certican®, Novartis)** will be dispensing in tablets in strength of 0.25, 0.5 and 0.75 mg.

Storage

*Oral solution of sirolimus:*
• Store in a refrigerator at 2°C - 8°C, in the original bottle in order to protect from light.
• If necessary, the patient may store the bottles at room temperatures up to 25°C for a short period of time (24 hours).
• Discard 30 days after opening the bottle.

*Tablets of everolimus:*
• Do not store above 25°C and keep the blister in the outer carton in order to protect from light.

4.5. Levels

• Trough (pre dose) mTOR inhibitors levels should be taken 3-7 days after starting treatment,
• The target serum trough level is 5 to 15 ng/mL for sirolimus, and 3 to 8 ng/mL for everolimus.
• Titrate the dose up or down by 0.25-0.5 mg/m²/day.
• Maximum dose is 3mg/m²/day for sirolimus and 5 mg/m²/day for everolimus.
• After any dose adjustment, recheck the trough level on day 3-7 after change.
• If glycaemic stability is not achieved (> 5% blood glucose measurement < 3.5 mmol/L in the UK, and at least one blood glucose < 3 mmol/L in France) and if there are no adverse effects, the dose may be increased after CHI MDT discussion to achieve target sirolimus levels of 10-15 ng/mL or everolimus to 9-15 ng/mL.

In rare instances, dose may be increased to a maximum trough level of 20 ng/mL.

• The trough serum sirolimus levels should be repeated every 7 days on maintenance treatment to ensure levels remain within therapeutic range.

• The efficacy of mTOR inhibitors cannot be judged until the patient has received 42 days of therapeutic treatment.

• On discharge from the hospital, mTOR inhibitors levels should be monitored every 28 days.

4.6. Monitoring

4.6.1. Blood glucose initially

Initially blood glucose monitoring must be done 1-2 hourly. The aim of successful treatment with sirolimus should be to achieve blood glucose > 3.5 mmol/L for > 90% of the time, i.e. 22 out of 24 measurements in a day (normal blood glucose is 3.5 to 7 mmol/L) in the UK, and > 3 mmol/L in all measurement in France, over a 48 hour period without requirement for intravenous fluids or glucagon therapy.

If glucose < 3.5 mmol/l is occurring frequently in spite of sirolimus being in the therapeutic range of 10-15 micrograms/l, discuss in MDT if sirolimus should be discontinued.

4.6.2. Inpatient Monitoring

<table>
<thead>
<tr>
<th>Daily</th>
<th>Twice Weekly</th>
<th>Weekly</th>
<th>fortnightly (UK only)</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Weight</td>
<td>Sirolimus Levels</td>
<td>Coagulation profile</td>
<td>Length / height</td>
</tr>
<tr>
<td>Infection profile</td>
<td></td>
<td>Neurumuscular examination</td>
<td>Thyroid Function Test</td>
<td></td>
</tr>
<tr>
<td>Blood Glucose</td>
<td></td>
<td>Oral cavity inspection</td>
<td>Test</td>
<td></td>
</tr>
<tr>
<td>Respiratory status</td>
<td></td>
<td>Full blood count</td>
<td>Faecal elastase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver / Renal Function Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lipid and Bone Profile</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 4.6.3. outpatient Monitoring

<table>
<thead>
<tr>
<th>Weekly</th>
<th>Monthly</th>
<th>Two Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone / e-mail review after discharge</td>
<td>Review by healthcare professional</td>
<td>Hospital admission for:</td>
</tr>
<tr>
<td>Discuss at CHI MDT</td>
<td>Sirolimus level</td>
<td>Blood glucose profile</td>
</tr>
<tr>
<td></td>
<td>Auxology</td>
<td>Blood tests</td>
</tr>
<tr>
<td></td>
<td>Full Blood Count</td>
<td>Continuous glucose monitoring</td>
</tr>
<tr>
<td></td>
<td>Liver Function Tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urea and Electrolytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipid Profile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone profile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Height and weight</td>
<td></td>
</tr>
</tbody>
</table>

- Monitoring data considered as abnormal:
  - Serum cholesterol levels > 5 mmol/L
  - Serum triglyceride levels > 1.5 mmol/L
  - Haemoglobin < 80 g/L
  - White blood cell < 2.5 x10⁹/L
  - Neutrophil polynuclear < 1.5 x10⁹/L
  - Platelet count < 150 x10⁹/L

### 4.7. Criteria for success of treatment (by 4-6 weeks of treatment):

- Achieving glycaemic stability with blood glucose > 3.5 mmol/l for > 90% of measurements in the UK, and > 3 mmol/L in all measurement in France, over a 48 hour period
- Decreased need for other treatment
  - For patient requiring IV glucose or glucagon:
    - no requirement for additional intravenous glucose supply or intravenous or subcutaneous glucagon infusions to maintain blood glucose
    - No indication for surgery
  - For patients with oral or enteral high carbohydrate diet:
• Ability to tolerate longer fast
• Decreased dose of diazoxide/somatostatin analogues compared with baseline
• No significant adverse events from mTOR inhibitor treatment

4.8. Discontinuation criteria

• If any of the following develop, treatment with sirolimus should be discontinued:
  - Increasing tachypnea
  - Desaturations
  - Requirement for supplemental oxygen
  - Increased work of breathing
  - Chest infection
  - Mouth ulcers
  - Abnormal full blood count which requires transfusion
  - Clinically significant abnormal liver function or coagulation profile
  - Deterioration in renal function
  - Altered lipid profile.

If thyroid function becomes abnormal, discuss with MDT team to consider additional treatment.

• If success criteria are not achieved by six weeks of therapy, sirolimus should be discontinued.
4.9. Side Effects / Interactions

- Patients and parents/guardians must be informed of all potential side-effects of mTOR inhibitors therapy before administration of the first dose:

<table>
<thead>
<tr>
<th>Common</th>
<th>Occasional</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Haemolytic uraemic Syndrome</td>
<td>Lymphoedema</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Neutropenia</td>
<td>Pulmonary haemorrhage</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypersensitivity reactions</td>
<td>Hepatic Failure</td>
</tr>
<tr>
<td>Gastric disturbances</td>
<td>Pericardial effusion</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Nausea</td>
<td>Venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Pleural effusion</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Ascites</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Stomatitis</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Interstitial lung disease</td>
<td></td>
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<tr>
<td>Hyperglycaemia</td>
<td></td>
<td></td>
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<tr>
<td>Hypokalaemia</td>
<td></td>
<td></td>
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<tr>
<td>Hypo-phosphoremia</td>
<td></td>
<td></td>
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<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
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</tr>
</tbody>
</table>

- **Interactions**
Sirolimus/everolimus are metabolised by the liver. There is therefore at risk of interaction with inducers and inhibitors of the CYP3A4 enzyme. Before commencing treatment, liaise with a pharmacist to check for interactions.

Drugs that can be problematic include:
<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral</td>
<td>Altered plasma concentrations of sirolimus</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Higher concentrations of mycophenolic acid</td>
<td>Monitor for side effects and consider a reduction in mycophenolate dose if necessary.</td>
</tr>
<tr>
<td>Proton- pump inhibitors</td>
<td>Hypomagnesaemia</td>
<td>Avoid if possible. If not, monitor magnesium levels</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Reduced plasma serum concentration of sirolimus</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Significantly increased serum concentrations of sirolimus</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>May increase serum concentration of sirolimus</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Ciclosporin greatly increases sirolimus concentrations. Concurrent use for longer than 3 to 4 months possibly increases renal toxicity.</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>Grapefruit juice appears to increase the exposure to oral sirolimus.</td>
<td>Avoid grapefruit juice</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>Result in an increase in serum sirolimus concentrations</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Greatly decreases sirolimus concentrations</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>ACE- inhibitors</td>
<td>Angioedema has been reported</td>
<td>Avoid if possible.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Elevated sirolimus concentrations</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>Fish oil</td>
<td>May increase serum sirolimus concentrations</td>
<td>Monitor levels and adjust sirolimus dose accordingly</td>
</tr>
<tr>
<td>Budesonide/formoterol</td>
<td>Increased serum concentrations of budesonide and sirolimus.</td>
<td>Monitor levels and adjust sirolimus dose accordingly. Monitor for corticosteroid side effects.</td>
</tr>
</tbody>
</table>
5. Bibliography


