Sirolimus (Sarcoma)

Indication
Epithelioid haemangioendothelioma
Perivascular epithelioid cell tumour (PEComa)
NB. Sirolimus is not commissioned by NHSE for these indications. Alternative route of funding required.

ICD-10 codes
Codes with a prefix C49.9

Regimen details

Drug	Dose	Route
Sirolimus	5mg OD*	Oral

*Dose adjusted according to blood sirolimus level. Pre-dose trough levels. Target 15-20 ng/ml

Cycle frequency
Continuous

Number of cycles
Continued until disease progression or unacceptable toxicity.

Administration
Sirolimus is available as 1mg and 2mg tablets. Tablets should be swallowed whole as crushing, chewing or splitting tablets may alter bioavailability. **NB. 0.5mg tablets are available but are not bioequivalent to the 1mg and 2mg tablet strengths and should not be used**. Sirolimus may be taken with or without food but the absorption of sirolimus is affected by food therefore patients should be consistent in how they take sirolimus in relation to meals.

If a dose is missed or the patient vomits after taking their dose, the patient **should not** be given an additional dose. The patient should take the usual prescribed dose on the following day.

Grapefruit and grapefruit juice should be **avoided** whilst taking sirolimus.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential (no routine antiemetics required)

Additional supportive medication
Not routinely required

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Lipids	14 days
Glucose	14 days
Blood pressure	1 month
Urinary protein	1 month

Consider ECG if patient has significant cardiac history.

Investigations – pre subsequent cycles

Patients should be reviewed 2-4 weeks after commencing sirolimus and prior to each cycle thereafter.

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Lipids	Every 12 weeks
Glucose	Every 12 weeks
Pre-dose sirolimus trough level	See below

Consider periodic ECG if patient has significant cardiac history or palpitations
Periodic urinalysis to monitor for proteinuria.

Investigations – sirolimus level monitoring

Whole blood sirolimus trough levels (i.e. taken 24 hours post last dose) should be performed around 2 weeks after starting treatment then every 1 -2 cycles thereafter. Target range is 15-20ng/mL and levels take 7 to 14 days to reach steady state. Monitoring frequency should be increased in those with hepatic impairment (see below) and in patients taking CYP3A4 and or P-gp inhibitors concomitantly or if these are discontinued.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	≤ 3.0 x ULN
Sirolimus	If trough level not within range (15-20 ng/ml) then discuss with consultant as may need dose adjustment

Dose modifications

- ### Haematological toxicity

If neutrophils < 1.0 x 10^9/L or platelets < 75 x 10^9/L, hold sirolimus until recovery and check levels. If treatment is held for > 1 week consider a 1mg dose reduction if sirolimus levels allow.

- **Renal impairment**

No starting dose adjustment is required when administering sirolimus to patients with renal impairment or with end-stage renal disease on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. Discontinue sirolimus in patients with nephrotic syndrome.

- **Hepatic impairment**

In patients with moderate hepatic impairment, sirolimus whole blood trough levels be closely monitored – see below. In patients with severe hepatic impairment (bilirubin >3 x ULN), the maintenance dose of sirolimus should be reduced by approximately 50%.

In patients with moderate or severe hepatic impairment, monitoring should be performed every 7 days until 3 consecutive trough levels have shown stable concentrations of sirolimus after dose adjustment or after loading dose due to the delay in reaching steady-state because of the prolonged half-life.

- **Other toxicities**

Non-haematological toxicity grade ≥ 2, withhold until toxicity returns to grade 0-1

Adverse effects - for full details consult product literature/ reference texts

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea
Raised liver enzymes
Diabetes, proteinuria, pancreatitis, abdominal pain
Raised cholesterol, Hyperlipidaemia, low potassium, low phosphate
Raised blood lactate dehydrogenase, raised serum creatinine
Collections of lymph fluid, abdominal oedema, pleural effusion.
Changes to menstrual cycle including amenorrhoea and menorrhagia
Acne, rash, impaired healing

Significant drug interactions – for full details consult product literature/ reference texts

Sirolimus is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver
CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, diltiazem, verapamil, erythromycin, clarithromycin, ritonavir): avoid co-administration these may increase plasma concentrations of sirolimus. If unable to avoid co-administration, consider reducing the starting dose of sirolimus
Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of sirolimus.
Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to sirolimus.
P-gp inhibitors (e.g. Cannabidiol): avoid as inhibition of intestinal P-gp efflux can increase exposure to sirolimus. If concomitant use is unavoidable, monitor closely for toxicity.
Coumarin anticoagulants, e.g. Warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin or DOAC.

References

- Summary of Product Characteristics – Sirolimus accessed 6th May, 2025 via www.medicines.org.uk
- Stacchiotti et al. Activity of sirolimus in patients with progressive epithelioid hemangioendothelioma: A case-series analysis within the Italian Rare Cancer Network. Cancer. 2021 Feb 15;127(4):569-576.

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