Reference number: 2316
Publication date: 16 July 2026

Clinical commissioning policy:

Sirolimus in extracranial slow-flow vascular malformations refractory to standard therapies (all ages)

Summary

Sirolimus in extracranial slow-flow vascular malformations refractory to standard therapies (all ages) is recommended to be available as a routine commissioning policy within the criteria set out in this document.

Committee discussion

Clinical Panel considered the evidence base and recommended that this policy proceeds for routine commissioning. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed on the NHS England website.

What we have decided

NHS England has carefully reviewed the evidence to treat patients with extracranial slow-flow vascular malformations refractory to standard therapies with sirolimus. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed on the NHS England website.

Links and updates to other policies

NHS England has no other policies relating to the use of sirolimus in extracranial slow-flow vascular malformations refractory to standard therapies.

Plain language summary

About slow-flow vascular malformations

Slow-flow vascular malformations are inborn errors of formation of blood vessels caused by genetic mutations. The types of blood vessels affected in slow-flow vascular malformations include veins, lymphatics and capillaries. They do not involve the high pressure and blood flow of arteries. Slow-flow vascular malformations have been estimated to affect about 1-1.5% of the population and, although often present at birth, can develop at any age (Gallagher et al, 2022).

The way slow-flow vascular malformations develop over a patient's life is unclear. Patients are thought to be born with slow-flow vascular malformations and associated syndromes

which grow with them. As they grow, they cause compression and damage to surrounding structures. Slow-flow vascular malformations can affect any organ system. Patients with slow-flow vascular malformations may suffer with debilitating symptoms and complications including pain, swelling, ulceration, bleeding, blood clots, infection, disfiguration, organ failure, limb loss, and death (Kalwani et al, 2021, Markovic et al, 2021). Patients with slow-flow vascular malformations also demonstrate significantly poorer quality-of-life and mental health when compared to the general population (Pang et al, 2022). In addition, slow-flow vascular malformations carry significantly negative socio-economic impact due to the lifelong nature of the condition and the involvement of patients of relatively young age groups (Kim et al, 2017).

About current treatment

Treatment of symptomatic slow-flow vascular malformations is limited to supportive (such as compression hosiery) and medical measures (such as pain medication and antibiotics to treat episodes of infection), and invasive procedures (including excision or debulking surgery, sclerotherapy and cryotherapy). Supportive and medical measures are often not effective in providing satisfactory outcomes to patients with significant symptoms and thus invasive procedures are the mainstay of treatment for these patients. Intracranial slow-flow vascular malformations are managed differently to extracranial slow-flow malformations, often requiring neurosurgical intervention. This policy solely includes patients with extracranial slow-flow malformations.

Invasive procedures are ineffective in managing severe symptoms and complications in a small subset of patients, particularly those with lesions that are large and widespread or located within challenging anatomy or vital organs, major blood vessels and nerves. Any invasive procedure on these complicated malformations is either impossible or carries very high morbidity, often life-changing, and mortality risks. Patients that don't respond to standard therapies are often left with no effective treatment options. They may have to continue to suffer with the debilitating symptoms, accept extremely high-risk invasive procedures, seek compassionate use of unlicensed or research therapy of unknown efficacy and safety, or in some cases palliation.

For patients with extracranial slow-flow vascular malformations refractory to standard care there is no licenced treatment available.

About sirolimus treatment

The intervention is for the use of oral sirolimus (also known as rapamycin) in patients with extracranial slow-flow vascular malformations who are refractory to standard care. Sirolimus inhibits or blocks a protein known as the mammalian target of rapamycin (mTOR). This protein is involved in pathways which regulate several cell functions including growth, proliferation and metabolism. Sirolimus inhibits the mTOR pathway which is overactive as a result of genetic mutations in patients with certain slow-flow vascular malformations (Shimano et al, 2022).

Sirolimus is not licenced for the use in extracranial slow-flow vascular malformations, and therefore, use will be off-label.

Epidemiology and needs assessment

There is limited data on the prevalence and incidence of slow-flow extracranial vascular malformations with only estimates in the literature. Slow-flow vascular malformations are generally venous and lymphatic malformations with or without involvement of capillaries.

The incidence of venous and lymphatic malformations have been estimated at 1 to 2 in 10,000 and 1 in 4000 live births respectively (Behravesh et al, 2016). Anecdotal estimation from the specialist units in England, suggest that approximately 70 new patients with refractory, extracranial slow-flow vascular malformations would be eligible for sirolimus per year.

Implementation

NHS England will routinely commission sirolimus in accordance with the patient pathway for patients meeting all of the following inclusion criteria, and none of the exclusion criteria.

Inclusion criteria

Patients with a confirmed diagnosis of extracranial slow-flow vascular malformations who meet the following criteria:

- Refractory (as defined by worsening or no improvement in symptoms, complications, and/or lesion size) to standard therapies

and

- Sirolimus is felt by the MDT to be lower risk (to the patient) compared to other treatment options that are potentially life-changing or life-threatening

and

- Surgery is contra-indicated or surgery alone is considered to have unacceptable high risk

and

- There is at least one clinical feature that objectively indicates severe disease. Clinical features indicating severe disease could include any of the following:
  - Biochemical and/or clinical evidence of coagulopathy – active or at risk of persistent and/or recurrent bleeding and/or thromboembolism.
  - Documented episode of infection needing hospital admission, related to slow-flow vascular malformation pre
  - Evidence of impending or ongoing end organ failure related to slow-flow vascular malformation (e.g. airway, visceral organs, limbs, and cardiopulmonary).
  - Persistent severe pain as evidenced by visual analogue scores for pain.
  - Significant deterioration of quality of life evidenced by Rand 36-Item Short Form survey (SF-36) and/or EuroQoL five-dimension scale (EQ-5D).
  - Persistent enlargement of slow-flow vascular malformation measured on radiological imaging (ultrasound, CT or MRI).

Exclusion criteria

Patients who meet the following criteria are not eligible for treatment with sirolimus under this policy:

- Individuals with contraindications to sirolimus, as described in the Summary of Product Characteristics (SmPC)

Starting criteria

As recommended by the International Society for the Study of Vascular Anomalies, at least three of the following four speciality groups should regularly participate in these meetings:

- Dermatology
- Oncology
- Interventional Radiology
- Surgery (Vascular, Plastics, ENT, General Surgery etc)
- Other Physician (Paediatrics, Genetics, etc)

This multidisciplinary team (MDT) must also have access to at least a clinical nurse specialist and specialist pharmacist.

It is suggested that different MDTs can collaborate through established networks, such as the Segmental Overgrowth & Vascular Malformation Rare Disease Collaborative Network or the Mosaic Disorders Rare Disease Collaborative Network.

Patients need to have received adequate pre-treatment counselling, in the form of both written and verbal information. Where appropriate, this must include advice on contraception and the need to discuss any planned pregnancy with their medical team. Patients need to receive this information prior to starting treatment, to ensure they have adequate decision-making time.

As part of pre-treatment counselling, patients need to be given a named lead consultant and a clear point of contact in the prescribing centre should they have any concerns once they have started sirolimus. Clinicians need to ensure that all necessary baseline blood tests and imaging have been performed, as well as ensuring that patients have received all the necessary vaccinations prior to starting treatment. These baseline blood tests and vaccines are outlined in appendix 1.

Stopping criteria

Treatment will be stopped in patients who meet **any** of the following criteria:

- Serious adverse events including anaphylaxis **or**
- Unacceptable toxicity **or**
- Patient decision to stop treatment **or**
- No clinical or radiological response after 6 months of treatment as determined by an appropriate MDT[1] **or**
- After 2 years of treatment, a trial of sirolimus cessation must take place for at least 3-6 months to determine resurgence (symptomatically or radiologically). If there is symptomatic or radiological resurgence with objective measures of severe disease as described in the inclusion criteria of this policy, sirolimus may be restarted after specialist MDT discussion.

Dosing

Sirolimus is given as a tablet or syrup.

- For children (age <18 years old), the starting dose is 0.8 mg/m^2 twice a day rounded to the nearest 0.5mg. The dose should be titrated in 0.5mg increments to achieve a steady state serum trough level of 4-15ng/ml.

[1] Six months of treatment within the appropriate target serum range

- For adults (age 18 years and above) the starting dose is 0.8 mg/m^2 twice a day. The body surface area will be estimated based on the body weight in kilogram (kg). Dose to be titrated in 0.5mg increments to achieve a steady state serum trough level of 4-15ng/ml.

Caution is advised when switching between tablet and liquid formulations due to varying bioavailability.

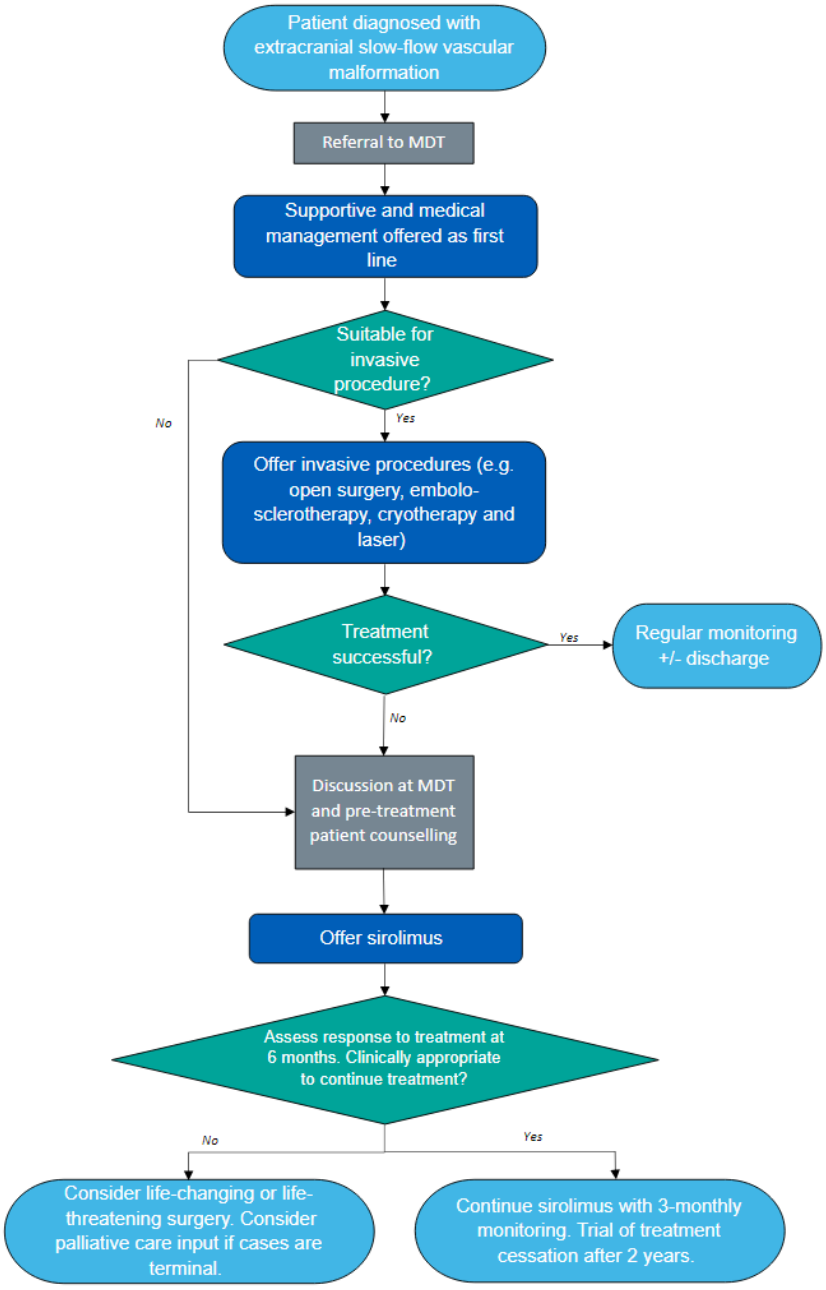
Monitoring

A formal medical review to assess blood tests (including sirolimus trough blood level) and to discuss the acceptability of side effects should take place within 2 weeks of starting treatment. Subsequently, it is advised for one monthly blood tests and medical review. At 3 months, providing the patient is felt to be stable, frequency of blood tests and medical reviews can be reduced to a minimum of every 3 months based on clinical judgement. The need for repeat imaging is acknowledged and is performed at intervals as decided by the lead clinician. Paediatric patients must be monitored in an experienced paediatric centre.

There is an acknowledgment that the risk and benefit of continuing sirolimus must be reviewed and discussed between the prescribing clinician and the patient. Issues include immunosuppression, future risks of malignancy, and risks around pregnancy and conception.

This treatment is off-label with a lack of evidence for safety and clinical effectiveness in long-term use for this indication.

Patient pathway



Governance arrangements:

This policy should be used in conjunction with the following service specifications:

Specialised Vascular Service Specification 170004/S

Paediatric Surgery: Surgery (and Pathology, Anaesthesia & Pain) E02/S/a

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine

is prescribed. These arrangements may be through the Trust's Drug and Therapeutics committee (or similar), and NHS England may ask for assurance of this process.

Please note that this is an off-label use of sirolimus, therefore Trust policy regarding unlicensed medicines should apply.

Mechanism for funding

Sirolimus maintenance within the criteria set out in this document will be commissioned and funded by NHS England under existing arrangements for the provision of specialised services.

Audit requirements

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. Clinical data should be submitted for audit purposes as part of the Rare Disease Collaborative Networks (RDCN). This information is collected to inform future policy revisions.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment, and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Definitions

Cryotherapy	A treatment using cold temperatures to remove lesions.
Refractory	Worsening or no improvement in symptoms, complications, and/or lesion size.

Sclerotherapy	A form of treatment where a special liquid or foam is injected into vessels, causing them to be sealed closed.
Slow-flow vascular malformation	An abnormality in the vessels including capillaries, veins and lymph.

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Appendix 1

Ensuring following vaccines are up to date: • Haemophilus • Pneumococcus • Meningitis B and C
Baseline blood tests: • Full blood count • Urea and electrolytes • Liver function tests • Clotting screen • Fasting cholesterol and triglycerides • HbA1c • Thyroid function tests • Urine protein: creatinine ratio • Beta hCG where indicated
Specialist blood tests pre-therapy: • Viral screen: EBV, CMV, HIV, Hepatitis B and Hepatitis C

- Immunoglobulins
- Lymphocyte subsets
- Pneumococcal antibodies
- Tetanus antibodies
- VZV IgG
- QuantiFERON

If any of these blood tests are abnormal, please discuss with Immunology prior to starting sirolimus. If antibody levels are low, please give vaccines before starting (wait at least 4 weeks if live vaccine).