NHS England

NHS ENGLAND SPECIALISED SERVICES

CLINICAL PANEL REPORT

Date: 17th January 2024

Intervention: sirolimus

Indication: extracranial slow-flow vascular malformations refractory to standard therapies (all ages)

URN: 2316

Gateway: 2, Round 1

Programme: Internal Medicine

CRG: Vascular

Information provided to the Panel

Policy Proposition

Evidence Review completed by Solutions for Public Health

Clinical Priorities Advisory Group (CPAG) Summary Report

Evidence to Decision (EtD) Summary

Equalities and Health Inequalities (EHIA) Assessment

Patient Impact Assessment

Blueteq™ Forms – initiation and continuation

Policy Working Group (PWG) Appendix

This Policy Proposition recommends the off-label use of sirolimus in extracranial slow-flow vascular malformations refractory to standard therapies (all ages). Slow-flow vascular malformations are inborn errors of formation of blood vessels. They can affect any organ system, and patients may suffer with debilitating symptoms and complications including pain, swelling, ulceration, bleeding, blood clots, organ failure, limb loss and death. The current standard of care is limited to supportive and medical measures, such as compression hosiery, and invasive procedures that can be life and limb threatening, such as debulking surgery or cryotherapy. Approximately 70 people per annum would be eligible.

The proposition and the supporting evidence review were presented to Panel members. Five studies were included – one randomised trial, three open label single arm trials, and one prospective case series. No comparator evidence was identified. No cost effectiveness evidence was identified.

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The critical outcomes for clinical effectiveness were disease response, overall survival (OS), and symptom alleviation. Important outcomes reported were radiographical changes, organ specific disease response, activities of daily living (ADLs) and quality of life (QoL). The presentation to Panel members covered all elements of the evidence.

Disease response – one study reported a statistically significant higher proportion of patients were classed as having a partial disease response compared to progressive or stable disease. Varied in response was seen between studies. Panel members noted that the Policy Working Group consider this partial response is a beneficial clinical response and a desirable outcome for patients.

A statistically significant improvement was reported in pain scores for adults, though not in children. A statistically significant decrease in functional disability was seen in children.
The randomised trial reported a statistically significant improvement in skin and subcutaneous disease resolution in children, using a visual analogue scale.

Evidence of a statistically significant increase in QoL scores for both children and adults were reported following at least six months of treatment with sirolimus.

Panel members noted that a lot of adverse events were reported across all five studies, although most were not classed as severe. Pre-treatment counselling is important for patients to make an informed decision before starting treatment. Administering this medicine needs to be considered and balanced with the limited evidence, particularly as this is recommended for all ages.

Limitations of the studies presented were discussed including the lack of comparator groups, lack of blinding, and lack of clarity around some of the population details included.

The evidence presented across all critical and important outcomes was reported as very low using modified GRADE. Panel members acknowledged and discussed the very low certainty evidence in a very small population however, they agreed that clinical benefits and beneficial outcomes were evidenced across the critical and important outcomes.

The proposition and supporting documents were considered and some amendments requested.

Panel members considered that the role of the multi-disciplinary team is very important in the decision-making process. Panel considered it is currently unclear who will be responsible for the management of these patients on a day-to-day basis as this is complex treatment. Sufficient safeguards need to be considered and put in place.

EHIA – an amendment required.
PIA – no amendments requested.

Recommendation

Clinical Panel agreed that this proposition and supporting documentation should return to a future meeting.

Why the panel made these recommendations

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Panel members agreed that there are a number of areas that need careful consideration and clarifying within the proposition, particularly regarding conditions for use, before a decision can be made as to whether this should progress as a routine commissioning position or not.

Documentation amendments required

General:

- The highly specialised services team should help facilitate a view from the Rare Diseases Network once the documentation has been further worked on.
- PWG members to be reviewed and expanded to ensure it includes more clinicians who have a lot of experience using this treatment.

Policy Proposition:

- Reference to Kasabach-Merrit syndrome is not currently in the proposition which a Panel member considered a subgroup of this proposition population. Check if the PWG have considered the inclusion of this syndrome.
- Current treatment – the reference to medical measures – it is unclear what this is.
- Implementation –
    - It needs to be clear who is responsible for the management of these patients on a day-to-day basis.
    - MDT – need to ensure there is sufficient expertise within this group. The expected constitution of this group is not sufficiently clear. PWG to consider inclusion of a dermatologist.
    - Inclusion criteria – need to be reviewed and ensure they are as strict as possible as this is high risk treatment.

Blueteq™ Form:

- The forms need to be sufficiently detailed in the requirements for access, such as biochemical monitoring and necessary vaccinations, and include the criteria relating to the indication of severe disease.

EHIA:

- Reference is made to the requirement for travel and the impact of such costs and local teams should work together to facilitate access. Suitable consistent guidance needs to be given to ensure everyone has access rather than leave it to local decision. This needs to refer to the national Healthcare Travel Cost Scheme.

Declarations of Interest of Panel Members: None received.

Panel Chair: James Palmer, Medical Director, Specialised Services

Post Panel Amendments

General comments		
Panel Comment	**Amendment**	**Page number (if applicable)**
The highly specialised services team should help facilitate a view from the Rare Diseases Network once the documentation has been further worked on.	We have included a suggestion that different MDTs can collaborate through established networks, such as the Systematic Overgrowth & Vascular Malformation Rare Disease Collaborative.	

FINAL

PWG members to be reviewed and expanded to ensure it includes more clinicians who have a lot of experience using this treatment.	There are current PWG members who prescribe sirolimus regularly. PWG members were reviewed, with an additional 5 members as described in the PWG appendix document. They all have direct experience prescribing and following up patients taking sirolimus from both an adult and paediatric perspective.	N/A
Policy Proposition		
Panel Comment	**Amendment**	**Page number (if applicable)**
Reference to Kasabach-Merritt syndrome is not currently in the proposition which a Panel member considered a subgroup of this proposition population. Check if the PWG have considered the inclusion of this syndrome.	The PWG feel that Kasabach-Meritt syndrome is caused by a subgroup of vascular tumours. Vascular tumours were not included in the evidence review and therefore out of the scope of this policy.	N/A
Current treatment – the reference to medical measures – it is unclear what this is	The wording has been amended to make clear that medical measures include pain medication and antibiotics to treat episodes of acute infection.	p3
It needs to be clear who is responsible for the management of these patients on a day-to-day basis.	Have added in the sentence '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.'	p5
MDT – need to ensure there is sufficient expertise within this group. The expected constitution of this group is not sufficiently clear. PWG to consider inclusion of a dermatologist	The constitution of the MDT has been reviewed and amended according to the International Society for the Study of Vascular Anomalies MDT constitution requirements. This includes a dermatologist.	p5
Inclusion criteria – need to be reviewed and ensure they are as strict as possible as this is high risk treatment.	Inclusion criteria were rediscussed by the PWG including by the additional members. The PWG felt that the inclusion criteria were as strict as could	

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	be without resulting in patient harm. However, amendments were made to the MDT requirements and governance to make clear the level of expertise required.	
Blueteq		
The forms need to be sufficiently detailed in the requirements for access, such as biochemical monitoring and necessary vaccinations, and include the criteria relating to the indication of severe disease.	The policy proposition document now has an appendix 1 which lists blood tests and vaccines required in full. The Blueteq refers to this appendix.	
EHIA		
Reference is made to the requirement for travel and the impact of such costs and local teams should work together to facilitate access. Suitable consistent guidance needs to be given to ensure everyone has access rather than leave it to local decision. This needs to refer to the national Healthcare Travel Cost Scheme.	Wording has been reviewed and amended throughout the document.	N/A

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