

National Institute for Health and Care Excellence

Health Technology Evaluation

Sirolimus gel for treating facial angiofibroma from tuberous sclerosis complex in people 6 years and older (review of TA972) [ID6757]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Plusultra pharma UK Ltd	We agree with the method of evaluation (STA).	Thank you for your comment.
	The Tuberous Sclerosis Association	Tuberous Sclerosis Association agrees with NICE that the treatment should be evaluated through its Single Technology Appraisal process.	Thank you for your comment.
	British Association of Dermatologists	This evaluation is appropriate as a STA; it offers the option of an effective and easy-to-use treatment for a very common problem in individuals with tuberous sclerosis complex (TSC).	Thank you for your comment.
Wording	Plusultra pharma UK Ltd	Yes, this remit reflects the clinical issues.	Thank you for your comment.

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	The Tuberous Sclerosis Association	Tuberous Sclerosis Association supports the wording of the remit as set out in the draft scope.	Thank you for your comment.
	British Association of Dermatologists	Yes [the wording is appropriate].	Thank you for your comment.
Timing issues	Plusultra pharma UK Ltd	<p>Currently, there are no authorised medicines to treat facial angiofibroma available. By introducing sirolimus, the patient journey will be substantially simplified as the product is planned to be available directly from local pharmacies. This change will result in less travel for patients.</p> <p>There is a substantial lack of guidance around treating TSC-associated facial angiofibroma. The composition of best supportive care comparator treatments listed in the draft scope are relevant, albeit there are issues around the appropriateness of these treatments for particular patient groups, the degree of invasiveness (a gel being less invasive than the comparative procedures), and issues surrounding the accessibility of current treatments, such as laser therapy, due to UK regional inconsistencies with whether the treatment is available.</p>	Thank you for your comment. This topic has been entered into the schedule.
	The Tuberous Sclerosis Association	<p>Tuberous Sclerosis Complex (TSC) associated facial angiofibroma have been reported in up to 74.5% of paediatric TSC patients, rising to up to 88% in adults >30 years old.</p> <p>The facial appearance resulting from facial angiofibroma lesions is associated with high psychological and physical morbidity (for example, recurrent bleeding or nasal obstruction), as such it may be considered alongside acne vulgaris, port wine stains, atopic dermatitis, congenital melanocytic nevi and other conditions as a psychodermatological condition with both physical and psychosocial impacts.</p>	Thank you for your comment. This topic has been entered into the schedule.

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		<p>The onset of facial dermatological conditions during school-age and adolescence has been found to cause a particularly negative psychosocial impact at a time when peer relationships gain importance and self-concept matures.</p> <p>Therefore, Tuberous Sclerosis Association considers this an urgent topic that should be appraised as soon as possible.</p>	
	British Association of Dermatologists	<p>There are no similar equivalent licensed treatments for facial angiofibromas in tuberous sclerosis complex (TSC). Facial angiofibromas cause significant distress and impact on quality of life (QoL) associated with erythema, lesions, potential disfigurement, etc., so there is a pressing need to address.</p> <p>There is inequity of care as some patients have historically been able to access an unlicensed “special” but this has been more difficult to access with the existence of a licensed therapy. Evaluating this via NICE would clarify how best to proceed with treating patients and improve equity of access.</p>	Thank you for your comment. This topic has been entered into the schedule.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Plusultra pharma UK Ltd	All information supplied is appropriate.	Thank you for your comment.
	The Tuberous Sclerosis Association	Please include the reference that facial angiofibroma are considered one of the key diagnostic criteria for TSC (Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, et al.	Thank you for your comment. The background section references that facial angiofibroma are considered one of the

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		Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. <i>Pediatr Neurol.</i> (2021) 123:50–66. doi: 10.1016/j.pediatrneurol.2021.07.011).	key diagnostic criteria for tuberous sclerosis complex. No change to scope required.
	British Association of Dermatologists	The information is accurate and complete.	Thank you for your comment.
Population	Plusultra pharma UK Ltd	Yes, this is appropriately defined.	Thank you for your comment.
	The Tuberous Sclerosis Association	Tuberous Sclerosis Association considers the population to be defined correctly.	Thank you for your comment.
	British Association of Dermatologists	Yes [the population is appropriate].	Thank you for your comment.
Subgroups	Plusultra pharma UK Ltd	The subgroups that may be of interest is that of children (aged 18 years or less) and adults (aged 19 years and older).	Thank you for your comment. Subgroups should be preferably identified because of known, biologically plausible mechanisms, social characteristics, or other clearly justified factors. Unless specified in the marketing authorisation,

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			the committee cannot make recommendations based on age because it is a protected characteristic. However, this does not prevent the identification of subgroups later in the process.
	The Tuberous Sclerosis Association	Tuberous Sclerosis Association agrees that subgroups by age should be considered.	Thank you for your comment. Subgroups should be preferably identified because of known, biologically plausible mechanisms, social characteristics, or other clearly justified factors. Unless specified in the marketing authorisation, the committee cannot make recommendations based on age because it is a protected characteristic. However, this does not prevent the identification of subgroups later in the process.

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	British Association of Dermatologists	No – appropriate for use in the whole population.	Thank you for your comment.
Comparators	Plusultra pharma UK Ltd	<p>There are no established, standardised clinical protocols for treating angiofibroma, as management is highly individualised based on the size, number of lesions, and patient tolerance. Therefore, we would argue that there are no current comparators available.</p> <p>However, we do understand that the listed comparators in the NICE draft scope are used in clinical practice.</p> <p>We do agree with the listed comparators with that element considered such that they may be considered a ‘bundled’ best-supportive care grouping, rather than individual comparators.</p>	Thank you for your comment.
	The Tuberous Sclerosis Association	<p>Tuberous Sclerosis Association believes all relevant comparators have been included in the draft scope.</p> <p>However, we note that access to these interventions varies considerably between areas and centres, and some procedures may not be routinely available locally.</p> <p>The evaluation should also recognise that:</p> <ul style="list-style-type: none"> • procedures are often repeated multiple times • treatments may require anaesthesia or sedation • procedures can be painful and distressing • scarring risk is an important consideration for patients and families <p>In practice, some patients may receive no active treatment because available interventions are considered too invasive, inaccessible, or burdensome.</p>	Thank you for your comment.

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	British Association of Dermatologists	Yes they are, although in practice, many of these would not be used routinely due to difficulty in access, e.g. for laser treatment, or due to difficulties treating this group of patients who often have learning difficulties which can make using physical treatments extremely challenging or impossible.	Thank you for your comment.
Outcomes	Plusultra pharma UK Ltd	The clinical effectiveness available from the RCT and OLE is not based on the 'number of tumours' – it is based on size and redness of the tumours instead. We believe this to be an appropriate measure of effectiveness.	Thank you for your comment. Redness of tumours has been added to this outcome for clarity.
	The Tuberous Sclerosis Association	Tuberous Sclerosis Association suggest that the following relevant outcome measure is added to the scope to differentiate it from the health-related quality of life of the patient: <ul style="list-style-type: none"> Caregiver health-related quality of life 	Thank you for your comment. Caregiver health-related quality of life is covered by the outcome 'health-related quality of life'. The company or other stakeholders may provide evidence of such benefits, if relevant, and the committee will consider them.
	British Association of Dermatologists	Yes – all three outcomes are appropriate. Whilst many aspects of TSC are not amenable to therapy, improving the appearance of facial angiofibromas with a topical gel can offer an effective treatment and greatly improve QoL. Patient satisfaction and physician global assessment was measured as general improvement by Wataya-Kaneda et al. 2017 .	Thank you for your comment.

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Equality	Plusultra pharma UK Ltd	<p>It is anticipated that this treatment will have a disproportionate impact for people with autism spectrum disorder (ASD). ASD is highly prevalent in people with TSC-associated FA. ASD and TSC are driven by the same genetic defect (mutations in the TSC1 or TSC2 gene). ASD is considered a protected characteristic under the UK Equality Act 2010.</p> <p>This consideration is particularly relevant when it comes to comparator treatments, such as invasive and sensory procedures (laser or photodynamic therapy) for people with ASD due to increased risk of sensory-sensitivity problems. To note, we do not anticipate any difference in efficacy between those with ASD and those without.</p>	Thank you for your comment. These equality issues will be noted and considered by the committee.
	The Tuberous Sclerosis Association	<p>The Tuberous Sclerosis Association believes specific parameters must be broadened to ensure that key subgroups within the Tuberous Sclerosis Complex (TSC) community are not unfairly disadvantaged or excluded. These include:</p> <ol style="list-style-type: none"> 1. Adverse impact on individuals with neurodevelopmental and behavioural disabilities <p>Up to 90% of individuals with TSC live with Tuberous Sclerosis-Associated Neuropsychiatric Disorders (TAND) including learning difficulties and challenging behaviours, making the standard invasive treatments painful and particularly distressing for both the individuals and their families.</p> <p>The currently improvised cream (crushed tablet in paraffin) is reported to be greasy, causing additional dermatological issues such as acne, and its consistency difficult to tolerate for those with sensory issues. The formulation and tolerability of treatment may significantly affect adherence, particularly in</p>	Thank you for your comment. These equality issues will be noted and considered by the committee.

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		<p>children and individuals with sensory sensitivities. Feedback from parents and families indicates difficulty with daytime application, forcing them to restrict treatment to a disruptive nighttime window where even then, the cream is rubbed off onto bedsheets.</p> <p>We recommend the scope accounts for patients with TSC who have a diagnosis of TAND - ASD, and sensory processing issues; and the practical administration barriers, when weighing the benefits of a purpose-built gel over invasive and/or poorly tolerated alternatives.</p> <p>2. Psychosocial burden and impact on mental health Families and members of the TSC community have reported that visible, bleeding facial lesions trigger bullying, social exclusion, and mental health challenges like anxiety, low self-esteem and depression during childhood's critical developmental windows. Crucially this does not depend only on the physical size or number of lesions, as even a small cluster of central facial lesions can cause emotional scarring.</p> <p>Alongside physical lesion count and size, we recommend the scope considers the psychosocial impact and the patients long-term mental and emotional well-being.</p> <p>3. Educational impact and long-term equity Parents report the self-consciousness and bullying experienced by children and young people with visible lesions directly impacts the child's anxiety, reduced classroom participation, and missed school. Experiencing these</p>	

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		<p>disruptions during foundational schooling years inflicts an unfair disadvantage which can compromise a child's long-term academic attainment and future life opportunities.</p> <p>We recommend the scope recognises educational disruption, school and social anxiety in line with the broader societal and quality of life impact.</p> <p>4. Socioeconomic and geographic inequality Access to the existing unlicensed topical treatment currently relies on slow and inconsistent Individual Patient Funding Requests (IPFR), resulting in a "postcode lottery" where families in restrictive regions are unfairly denied treatment.</p> <p>We recommend the scope recognises these geographic and socioeconomic inequalities across the country.</p> <p>5. Impact on the caregiver and wider family unit</p> <p>Managing a child or adult with a rare, complex, multi-system genetic condition - especially when navigating bleeding facial lesions alongside challenging TAND behaviours and learning difficulties can place substantial emotional and practical strain on the wider family.</p> <p>We recommend the scope recognises the impact on caregiver and wider family quality of life. This is particularly relevant in paediatric patients and</p>	

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		individuals with TAND who may require substantial caregiver support for treatment administration and healthcare attendance.	
	British Association of Dermatologists	<p>The proposed treatment would be inclusive for any person with facial angiofibromas and would not impact on specific groups with protected characteristics.</p> <p>However, it is important to consider learning difficulties and cognitive impairment (e.g. Tye et al., 2020) as protected characteristics under the Equality Act and are common in patients with TSC. Excluding this population from the scope would inevitably result in a disadvantage for these patients, given the challenges in providing other forms of intervention.</p> <p>Another protected characteristic includes socioeconomic status. Currently, unlicensed sirolimus is only available in some trusts, which may necessitate additional costs and time (e.g. off work or school) for traveling. Whilst this will affect all patients regardless of their socioeconomic status, those in poverty will be more significantly impacted.</p> <p>Patients with tuberous sclerosis are often cared for in specialist multidisciplinary clinics. It would be ideal if the treatment could be prescribed locally (e.g. in primary care) once it has been recommended or initially prescribed by a member of the tuberous sclerosis service. Prescribing at some centres is currently being done by nurse prescribers.</p> <p>The treatment is generally well tolerated without systemic adverse events related to the treatment (blood sirolimus levels were detected in a small proportion of study participants and they were below levels that were deemed immunosuppressive - Leducq et al. 2019 and Lin et al. 2022).</p> <p>Finally, erythema is often underestimated in people with skin of colour.</p>	Thank you for your comment. These equality issues will be noted and considered by the committee.

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Other considerations	The Tuberous Sclerosis Association	A topical gel formulation may reduce the cumulative burden associated with repeated hospital visits, invasive dermatological procedures, sedation and recovery time.	Thank you for your comment.
	British Association of Dermatologists	<p>It must be expressed that prescribing should not be limited to specialist centres only; ongoing prescribing needs to be available in secondary care services, or ideally, as an option for recurrent prescribing in primary care with a rebate scheme if indicated (as a low technology intervention, topical therapy with limited monitoring/adverse effects). Otherwise, this reduces capacity of specialist services to see new patients.</p> <p>Making sirolimus more widely available (i.e. secondary or primary care) would minimise unnecessary travel for affected patients and families. This may be especially helpful for patients with autism or cognitive impairments which often can make travelling challenging.</p> <p>In addition, patients with TSC often have multiple other hospital appointments as part of their multidisciplinary care. Currently, for those accessing an unlicensed special, supply is often interrupted for these patients as they can only access it from their secondary care provider as a special, the practicalities of this leads to delays.</p>	Thank you for your comments. Please note that decisions regarding prescribing do not fall within NICE's remit.
Questions for consultation	Plusultra pharma UK Ltd	<p>(Q1) Where do you consider sirolimus gel will fit into the existing care pathway for facial angiofibroma? (Answer) Prescribed in secondary care with routine follow-up in primary care.</p> <p>(Q2) For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.</p>	Thank you for your comments.

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		<p>(Answer) All comparator treatments take place in secondary care. We would anticipate that follow-up appointments after the procedures would take place in secondary care as well.</p> <p>(Q3) Would sirolimus gel be a candidate for managed access? (Answer) No.</p> <p>(Q4) Do you consider that the use of sirolimus gel can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.</p> <p>(Answer) There is a published case study titled 'Facial Angiofibromas in Tuberous Sclerosis Complex: A Patient Case Study' by the British Dermatology Nursing Group in the Spring 2026 (volume 25, issue 1) that reports the wider impact on the family of people with TSC, particularly the impact of FA.</p> <p>Further, the study by Monaghan et al. (2022) highlights the substantial impact on carers of people with FA.</p>	
	British Association of Dermatologists	<p>Where do you consider sirolimus gel will fit into the existing care pathway for facial angiofibroma?</p> <p>→ Topical sirolimus should come before procedural treatment options, especially in the context of TSC where many of those affected have learning difficulties and cognitive impairment, and also because it is hoped that treatment will begin in childhood.</p>	Thank you for your comments.

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		<p>Please select from the following, will sirolimus gel be:</p> <ul style="list-style-type: none"> A. Prescribed in primary care with routine follow-up in primary care B. <u>Prescribed in secondary care with routine follow-up in primary care</u> C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): <p>For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.</p> <p>→ Procedural treatments are often office- or outpatient-based which would involve travelling by patients and their carers. Topical treatments can be prescribed either in primary or secondary care, and even if prescribed in secondary care, it may be possible to arrange for the topical treatment to be delivered to the patients or obtained from their local pharmacy. Follow-up for procedural treatments may be needed, especially if there are complications. Follow-up for topical treatments may be shared between primary care and secondary care. especially if repeat prescriptions can also be obtained via primary care.</p> <p>Would sirolimus gel be a candidate for managed access?</p> <p>→ No – it should be under routine commissioning rather than highly specialised or managed access from a clinical evidence and efficacy perspective, and to aid access. The Scottish Medicines Consortium (SMC) has approved under routine commissioning. Sirolimus is also on the orphan medicines list.</p>	

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		<p>Do you consider that the use of sirolimus gel can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?</p> <p>→ Yes, the use of topical sirolimus gel may result in substantial health-related benefits that are unlikely to be fully captured in the QALY calculation. These include improved cosmetic outcomes, which can significantly enhance a patient's psychological / psychosocial well-being, especially for individuals with visible facial angiofibromas.</p> <p>The non-invasive nature of the treatment reduces the need for repeated ablative laser procedures under general anaesthesia, thereby minimising the associated risks and burdens for patients with multisystem disease.</p> <p>Additionally, sirolimus gel may lower the risk of complications such as bleeding or infection from untreated angiofibromas, contributing to better overall quality of life beyond what is typically measured in QALY assessments.</p> <p>Finally, QALY calculations are unlikely to factor in the impact on carers. TSC has a significant impact on families' QoL where the possibility of medical emergencies, new symptoms, surgeries and treatment adverse effects would be constantly at the back of their minds. TSC-related behavioural issues would also have an impact on family dynamics. Parents may need to give up work which will have financial implications.</p> <p>Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.</p> <p>→ Watanabe-Kaneda et al. 2018 measured changes in DLQI and cDLQI in study participants. QoL was the subject of another study of 33 participants by Hatano T et al. 2020.</p>	