sirolimus gel (Hyftor®)

Plusultra pharma

06 December 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

sirolimus (Hyftor®) is accepted for use within NHSScotland.

Indication under review: for the treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older.

In a randomised phase III study, sirolimus gel demonstrated a statistically significant improvement in facial angiofibromas at week 12 compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Sirolimus binds to the specific cytosolic protein FKPB-12, and this complex inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a critical kinase for cell cycle progression. The inhibition of mTOR results in blockage of several specific signal transduction pathways. The net result is the inhibition of lymphocyte activation, which results in immunosuppression.[1] The exact mechanism of action of sirolimus in the treatment of angiofibroma in tuberous sclerosis complex (TSC) is not known. Sirolimus gel should be applied to the affected area twice daily (in the morning and at bedtime); a dose of 125 mg gel (or 0.5 cm gel, corresponding to 0.25 mg sirolimus) should be administered per 50 cm^2 lesion in the face. If no treatment effect is experienced, treatment with sirolimus gel should be discontinued after 12 weeks. See Summary of Product Characteristics for more details.[2]

1.2. Disease background

Tuberous sclerosis complex is an autosomal dominant genetic disorder that is primarily caused by mutations in genes TSC1 and TSC2, which are involved in cell growth regulation.[3] The mutations lead to constitutive activation of the mTOR signalling pathway, which results in abnormal proliferation, differentiation, and migration of cells. These cause growth of numerous noncancerous tumours (or tubers) in different parts of the body including the skin. The prevalence of TSC in Europe is between 1 in 25,000 to 1 in 11,300.[4] Facial angiofibroma is the most common skin condition associated with TSC, affecting approximately 86% of patients; angiofibromas generally become noticeable at around the age of 5 years.[5] Facial angiofibromas can spontaneously bleed, impair eyesight and cause aesthetic disfiguration. Although benign, facial angiofibromas can have a detrimental psychological impact on patients, causing emotional distress or social isolation.[1, 6]

1.3. Treatment pathway and relevant comparators

Treatment and monitoring of TSC-related skin lesions is recommended for lesions that rapidly change in size or number, cause functional interference, cause pain or bleeding, or inhibit social interactions. Many patients can experience benefits in TSC-related skin lesions by taking systemic mTOR inhibitors such as everolimus, which are prescribed to treat other manifestations of TSC. However, systemic mTOR inhibitors are generally not prescribed to treat TSC-related skin lesions alone due to an unfavourable risk-benefit ratio. Topical sirolimus is recommended in international guidelines; unlicensed preparations have historically been prepared in specialist pharmacies, but the concentrations of these products are not standardised and have not been tested in controlled clinical studies. Off-label topical use of the licensed sirolimus oral solution also has not been tested in controlled clinical studies. Other interventions such as dermabrasion, laser therapy, surgical excision of lesions, radiofrequency ablation, and electrocoagulation, can have potential complications such as scarring, pigmentation disorders, post-operative infections or complications from general anaesthesia. Angiofibroma can also recur, or treatment benefit may be short lived. There may also be variation across Scotland in access to these treatments.[1, 5, 7]

1.4. Category for decision-making process

Eligibility for a PACE meeting

Sirolimus meets SMC orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of sirolimus for the treatment of facial angiofibroma associated with TSC comes from NPC-12G-1. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	NPC-12G-1[1, 8]
Study design	Randomised, double-blind, phase III study.
Eligible patients	• At least 3 years old. • "Definite diagnosis" of TSC (according to International TSC Consensus Conference 2012 criteria). • Patients with three or more reddish papules of facial angiofibroma (≥ 2 mm in diameter). • Patients were not suitable for therapy with laser or surgery for angiofibroma, or did not want laser therapy or surgery.
Treatments	Sirolimus gel (0.2% w/w) or placebo twice daily (morning and bedtime) evenly applied to lesions. The dose was 125 mg gel (approximately 0.5 to 1 cm as the length of gel extruded from the tube) per lesion of 50 cm^2. Maximum daily doses were 400 mg gel, 600 mg gel, and 800 mg gel for patients aged 5 years and younger, 6 to 11 years, and 12 years and older respectively. Treatment was to continue for 12 weeks or stopped in the case of need for surgical treatment of angiofibroma or failure to apply study medicine for at least 8 consecutive days.
Randomisation	Randomised in a 1:1 ratio. Stratified by age (<19 years or ≥ 19 years).
Primary outcome	Composite improvement in angiofibromas assessed using photographs by an IRC at 12 weeks. This assessment considered change in angiofibroma size, extension (shrinkage, flattening, disappearance) and angiofibroma redness, and was categorised into the following six categories: "markedly improved", "improved", "slightly improved", "unchanged", "slightly exacerbated", and "exacerbated".
Secondary outcomes	• Composite improvement in angiofibromas assessed using photographs by the IRC (alternative timepoints to primary outcome) • Composite improvement in angiofibromas assessed by the investigator • Improvement in the size of angiofibromas assessed by the IRC and the investigator • Improvement in the redness of angiofibromas assessed by the IRC and the investigator

	• Improvement in hypomelanotic macules and plaques on the head assessed by the IRC and the investigator • Proportion of patients assessed as "improved" or a better category in the primary outcome and in select secondary outcomes • Change in total score from baseline for DLQI and CDLQI. Secondary outcomes were assessed at 4 weeks, 8 weeks, and 12 weeks after the start of study medication and 4 weeks after the end of study medication.
Statistical analysis	Efficacy analyses were performed in the FAS, defined as patients with definitive registration, except those who had not received the study medicine and those for whom no information had been obtained on efficacy after the start of administration. No adjustment for multiplicity was performed; secondary outcomes can be considered descriptive only.

Abbreviations: CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; FAS = full analysis set; IRC = independent review committee; TSC = tuberous sclerosis complex.

Sirolimus gel demonstrated a statistically significant improvement in facial angiofibromas assessed by independent review committee (IRC) at week 12 compared with placebo (Table 2.2). Secondary outcomes also generally favoured sirolimus gel over placebo.[1]

Table 2.2. Results of the NPC-12G-1 study at week 12 (IRC-assessed).[1]

	Sirolimus gel (n=30)	**Placebo gel (n=32)**
Primary outcome: Composite AF improvement distribution		
Markedly improved	17%	0%
Improved	43%	0%
Slightly improved	37%	16%
Unchanged	3.3%	81%
Slightly exacerbated	0%	0%
Exacerbated	0%	0%
Not evaluated	0%	3.1%
p-value	<0.001	
Secondary outcome: Composite AF improvement		
Markedly improved or improved	60%	0%
Secondary outcome: Improvement in AF size at 12 weeks		
	60%	3.1%
Secondary outcome: Improvement in AF redness at 12 weeks		
	40%	0%
Post-hoc exploratory outcome: IFA mean total score change from baseline to 12 weeks (IEC)		
	-3.5 points	0.5 points

Abbreviations: AF = angiofibroma; IEC = independent evaluation committee; IFA = Index for Facial Angiofibroma; IRC = independent review committee.

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed by two questionnaires: Children's Dermatology Life Quality Index (CDLQI) and DLQI. The baseline scores of both questionnaires were low meaning there was little room for improvement. Changes from baseline in mean total scores for CDLQI and DLQI were small and no relevant differences between sirolimus and placebo were observed.[1]

2.3. Supportive studies

NPC-12G-2 was a multicentre, open-label, single-arm study that recruited patients aged 3 years or above with a definite diagnosis of TSC (as per International TSC Consensus Conference 2012) with angiofibromas, hypomelanotic macules, or plaques associated with TSC on the head. Patients from NPC-12G-1 could enrol but new patients could also be recruited. The aim of the study was primarily to investigate the long-term safety of sirolimus gel, however efficacy outcomes were also assessed. Ninety-four patients were enrolled, of whom 88 completed the 52-week assessment and 53 completed the 104-week assessment. Patients were treated with sirolimus gel 0.2% twice daily applied to angiofibroma lesions, hypomelanotic macules and plaques on the head. The main efficacy result assessed was the composite angiofibroma improvement (IRC-assessed). At week 12 the improvement rate (improvement or marked improvement) was 59%, increasing to 78% at week 52. DLQI and CDLQI scores were low at baseline and remained almost unchanged throughout.[1, 9]

3. Summary of Safety Evidence

In the NPC-12G-1 study, the mean duration of treatment was 87 days in the sirolimus gel group and 86 days in the placebo group. Any adverse event (AE) was reported by 90% of patients in the sirolimus gel group (27/30) and 69% in the placebo group (22/32), and these were considered treatment-related in 73% and 47%, respectively. Mild AEs were reported in 63% of both treatment groups; moderate AEs were reported in 27% and 6% of the sirolimus and placebo groups, respectively; skin irritation was reported in 80% and 47%. One patient receiving sirolimus reported two serious AEs; gastric haemorrhage (unrelated to treatment) and acute pancreatitis (treatment-related according to investigator). No AEs led to discontinuation of treatment in either group.[1, 8] In the NPC-12G-2 extension study, the rates of any AE (98%), treatment-related AE (77%), SAE (9.6%) and severe AEs (6.4%) increased compared to the NPC-12G-1 study. There were also 2 cases of AEs leading to discontinuation.[1, 9]

The most frequently reported treatment-related AEs of any grade with an incidence >5% in the sirolimus gel group versus the placebo group were: dry skin (37% and 13%); pruritus (17% and 13%); acne (6.7% and 0%); and application site irritation (37% and 28%).[1, 8]

Overall regulatory authorities concluded that sirolimus was generally well tolerated, with the most common side effects being local dermatological events mild to moderate in nature. However, the risk of systemic adverse reactions cannot be fully excluded.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Sirolimus gel (Hyftor®) is the first topical preparation of sirolimus licensed for the treatment of facial angiofibroma associated with TSC in adults and paediatric patients.
- Sirolimus gel showed a clinically relevant and statistically significant treatment effect on facial angiofibromas compared with placebo. In study NPC-12G-1, 60% of patients receiving sirolimus gel had markedly improved or improved at week 12 compared with 0% in the placebo group. Benefits were observed in both size and redness of angiofibromas.[1] In the open-label, single-arm, long-term extension study, the improvement rate (improvement or marked improvement) reached 78% at 52 weeks.[1, 9]

4.2. Key uncertainties

- No direct or indirect evidence has been presented comparing sirolimus gel with relevant comparators, including off-label and unlicensed sirolimus preparations, laser therapy and surgery. The submitting company indicated that generating comparative evidence against these interventions was not feasible due to the lack of supporting evidence for these interventions.
- Oral mTOR inhibitors are commonly used to treat a variety of TSC-related manifestations.[7, 8] An exploratory subgroup analysis of NPC-12G-2 (n=19) suggests there is no difference in treatment effect of sirolimus gel between those who are taking concomitant oral mTOR inhibitors, for other TSC-related complications, versus those who are not.[1]
- The primary outcome of NPC-12G-1 is not a formally validated outcome, measuring relative change from baseline in angiofibromas and does not consider absolute change. However, regulatory authorities noted there is no gold standard scale for evaluating facial angiofibroma. An absolute efficacy outcome (Index for Facial Angiofibroma mean total score change from baseline to week 12) was assessed post-hoc and although exploratory and unvalidated, the results appear to be consistent with the primary outcome.[1]
- Quality of life was measured using CDLQI/DLQI questionnaires which may not adequately capture the impact of facial angiofibromas on quality of life.[1] Although Study NPC-12G-1 was conducted only in Japan, facial angiofibromas associated with TSC are not expected to differ between Japanese and European patients.[1]

4.3. Clinical expert input

Clinical experts consulted by SMC acknowledged the value of a licensed topical preparation of sirolimus. They considered that it would be easier to prescribe and would be more widely available than the alternative off-label and unlicensed preparations.

4.4. Service implications

There are no service implications anticipated with the introduction of sirolimus gel.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of sirolimus, as an **orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- TSC is a rare genetic condition that causes growths (also known as benign tumours) to develop in different organs around the body. Facial angiofibromas are one type of these growths. Facial angiofibromas can appear at an early age and into adulthood, and have both physical implications (nasal obstruction, bleeding, pain, irritation/itching, infection, facial scarring and disfigurement) and psychological ramifications (emotional and self-confidence issues) which impact patients' quality of life. The onset of facial dermatological conditions during school-age and adolescence has been found to cause a particularly negative psychosocial impact. TSC-associated neuropsychiatric disorders are common and can include (but are not limited to) aggressive behaviours, autism spectrum disorders, anxiety, depression or intellectual disabilities known as TAND (Tuberous Sclerosis Associated Neuropsychiatric Disorders).

- Current approaches for management of facial angiofibromas include topical ointments and invasive treatments like dermabrasion, laser therapy and surgical removal of the large lesions. However, many patients also have learning difficulties and do not tolerate the sessions of laser therapy without multiple general anaesthetics. Laser therapy can also be painful leaving bruises and swelling, there is a risk of scarring, and has limited efficacy. Topical preparations of sirolimus are not commercially available in Scotland, therefore crushed tablets or oral solution of sirolimus have been used topically with beneficial effects in treatment of facial angiofibromas. PACE participants identified several issues with the off-label and unlicensed sirolimus preparations, including the texture of the product, the irritation caused to the skin, the time it takes for the cream to soak in to the skin, the short expiry dates on preparations, and the inconvenience of sometimes requiring lengthy travels to hospitals. Given the limitations of off-label sirolimus and the invasive treatment options, there is an unmet need for a licensed topical preparation of sirolimus.

- PACE participants consider topical sirolimus gel to have a pronounced beneficial effect on facial angiofibromas. It may maintain near-normal skin with daily use which may have a positive impact on patient's mental health and wellbeing. It is considered to be safe, well tolerated, and convenient. It could also have implications for the risk of bleeding and infections associated with facial angiofibromas. PACE participants suggested that the licensed product is less irritant and easier to apply than the greasy unlicensed preparations, which is particularly relevant in patients with TSC-associated behavioural issues, and may reduce the need for other topical treatments such as topical steroids .

- TSC has a huge impact on families' quality of life and on their ability to support the child's ability to reach an acceptable level of wellbeing. Family members and carers worry about the possibility of medical emergencies, new symptoms, surgeries, and side effects of treatments. Behavioural issues associated with TSC affect the relationships of the whole family . In many instances, parents have had to give up work to become full time carers which can have financial implications. The availability of sirolimus gel is expected to have a positive impact for family members and carers. With facial angiofibromas well-controlled, family members and carers would have one less issue to worry about. PACE participants described difficulty with obtaining prescriptions for off-label and unlicensed sirolimus. The approval of a licensed preparation of topical sirolimus would improve ease of access and would reduce the overall burden of medicine management for family members and carers.

- PACE participants agreed that the medicine should be used as per the licensed indication. There are no major differences anticipated with treatment delivery of sirolimus gel compared with off-label and unlicensed sirolimus preparations.

Additional Patient and Carer Involvement

We received a patient group submission from the Tuberous Sclerosis Association, which is a registered charity. The Tuberous Sclerosis Association has received 11.2% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from the Tuberous Sclerosis Association participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary of the economic analysis provided by the submitting company is outlined in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	The time horizon was 77.5 years, with an assumed mean starting age was 22.5 years.
Population	Adult and paediatric patients aged 6 years and above with facial angiofibroma associated with TSC.
Comparators	Best supportive care (BSC). BSC was defined as laser therapy as a primary intervention and photodynamic therapy surgical excision, cryosurgery and dermabrasion.
Model description	The submitting company presented a model combining a decision tree and a Markov structure. Both parts of the model contained the same states, with patients being either 'controlled', 'uncontrolled' or 'dead'. All patients started with uncontrolled symptoms, and patients were assessed after 12 weeks. In the sirolimus gel arm, patients who did not achieve control at the 12-week mark switched to BSC. A 2.04% discontinuation rate was applied in the first year. In the Markov phase, patients with controlled symptoms on sirolimus gel stayed on

	treatment until death, while those on BSC transitioned between controlled and uncontrolled states depending on temporary relief from laser therapy or surgery. The model cycles were initially based on study visits, with a standard 13-week cycle thereafter.
Clinical data	Clinical evidence applied in the economics was taken from the NPC-12G-1 study and the NPC-12G-2 extension study.[8, 9] These sources informed the starting age, cycle length and the transition probabilities in the sirolimus gel arm and BSC arm at 12 weeks. The discontinuation rate for sirolimus gel was that observed in the NPC-12G-2 study.
Extrapolation	The submitting company assumed that the clinical effectiveness of sirolimus gel was constant following the first year of the model. The only reason patients would exit the sirolimus gel treatment arm would be death. A standardised mortality ratio of 4.99, generalised from an analysis of long-term National Health Insurance collected in Taiwan[10], was used to inform the increased risk of mortality associated with TSC compared to the general UK population.[11]
Quality of life	Utility values were sourced from literature. The values from Dutta *et al.* 2023[12] were SF36 values and were mapped to EQ-5D values using the algorithm published by Ara *et al.* 2008[13]. AE disutility was not applied. The base case utility value for the controlled health states was 0.543 and 0.483 for the uncontrolled health states.
Costs and resource use	Costs included were acquisition costs and health state resource use. AE costs were not included.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

Base case results are presented below in Table 6.2. These are inclusive of the PAS discount on sirolimus gel. The key driver of costs was the acquisition cost of sirolimus gel, although this was estimated as being offset by lower resource use for sirolimus gel patients. Sirolimus gel was projected as leading to better health outcomes by having a higher and more sustained control over facial angiofibroma.

Table 6.2. Base case results (PAS price for sirolimus gel)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Sirolimus gel	£91,179	11.03	-	-	-
BSC	£76,087	10.21	£15,093	0.818	£18,456

Abbreviations: BSC = best supportive care; Incr. = incremental; ICER = incremental cost-effectiveness ratio; QALYs =quality-adjusted life years

6.3. Sensitivity analyses

Scenario analyses presented by the submitting company are shown below in Table 6.3. These results include the PAS discount on sirolimus gel.

Table 6.3 Scenario Analysis Results (PAS price for sirolimus gel)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			£15,093	0.82	£18,456
1	Time horizon	Lifetime	5 Years	£3,315	0.17	£19,475
2			50 years	£14,870	0.81	£18,424
3	Response assessment	12 weeks (RCT & Open-label)	12 weeks (RCT only)	£11,504	0.63	£18,197
4			52 weeks (RCT & Open-label)	£15,093	0.82	£18,456

5	Response threshold	Improved	Slightly improved	£21,362	0.98	£21,698
6	Discontinuation rate	Applied for the first year only	Applied across the full duration of the model	£11,194	0.616	£18,184
7	Utility values	Controlled utility value used in both BSC and sirolimus gel arms	Non-improved score applied across BSC arm	£15,093	0.94	£16,005
8	Sirolimus gel dosage	1 tube used every 4 weeks	1.3 tubes used every 4 weeks	£39,156	0.82	£47,881

Abbreviations: BSC = best supportive care; Incr. = incremental; ICER = incremental cost-effectiveness ratio; QALYs =quality-adjusted life years; RCT = Randomised controlled clinical trials

6.4. Key strengths

- The model structure was appropriate.
- The model was validated by experts.

6.5. Key uncertainties

- Clinical experts consulted by SMC highlighted that the most common treatment for the target population in Scotland was off-label sirolimus oral solution used topically and an unlicensed topical preparation. This comparator was not included in the economics. The submitting company argued that given the lack of efficacy and safety data for topical oral sirolimus, along with the fact that it is off-label or unlicensed in this indication, meant that it was an unsuitable comparator. There were advantages to a licensed treatment, however, a lack of comparison with current practice was a weakness of the presented economic case noted by the committee.
- The comparator treatment used in the model was BSC, but the efficacy of this relative to sirolimus gel was uncertain with no data from a direct or indirect comparison available. The chance of success from laser treatment and surgery were based on clinical expert opinion. Further, the duration of symptom relief following laser treatment or surgery was assumed to be 12 weeks, with no evidence provided in support of that value. Therefore, overall efficacy of BSC treatment is uncertain and may be underestimated.
- The submitting company assumed that the average treatment dosage of sirolimus gel would equate patients using one 10 g tube per 4 weeks. It looked to support this dosage based on real world data from a post-marketing general drug-use survey in Japan and from anecdotal evidence from UK clinicians experienced in prescribing sirolimus gel. However, the dosage received in the NPC-12G-2 study was higher, with an average of 1.3 tubes used per 4 weeks. This introduced some uncertainty on the usage that may be observed in Scotland. Aligning the usage in the model with that from the NPC-12G-2 study led to a large increase in the ICER (Scenario 8).

7. Conclusion

The Committee considered the benefits of sirolimus gel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland was satisfied. In addition, as sirolimus gel is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted sirolimus gel for use in NHSScotland.

8. Guidelines and Protocols

The Tuberous Sclerosis Association published guidelines "The UK guidelines for management and surveillance of Tuberous Sclerosis Complex" in September 2018.[5]

International Tuberous Sclerosis Complex Consensus Group (ITSCC) updated diagnostic criteria and surveillance and management recommendations in October 2021.[7]

9. Additional Information

9.1. Product availability date

01 November 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
sirolimus gel	**A dose of 125 mg gel should be administered per 50 cm^2 lesion in the face, twice daily. Maximum recommended daily dose, 600mg gel in patients aged 6-11 years; or, 800mg gel in patients aged ≥ 12 years**	**Patients aged 6-11 years, up to £8,800** **Patients aged ≥12 years, up to £12,000**

Costs from dm+d on 23 September 2024. Costs do not take any patient access schemes into consideration

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 232 patients eligible for treatment with sirolimus gel in each year. The estimated uptake rate was 25% in year 1 and 55% in year 5. This resulted in 58 patients estimated to receive treatment in year 1 rising to 128 patients in year 5.

Inclusive of the PAS discount on sirolimus gel, the gross medicines budget impact was estimated to be £257k in year 1 rising to £565k in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £228k in year 1 rising to £428k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 20 November 2024.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via

the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.