Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2405

berotralstat 150mg hard capsules (Orladeyo®)

BioCryst Pharmaceuticals

4 February 2022

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 equivalent process

berotralstat (Orladeyo®) is accepted for restricted use within NHSScotland.

Indication under review: routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

SMC restriction: patients who experience ≥ two clinically significant attacks per month.

In a phase III study in patients with HAE, berotralstat reduced the attack rate 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.

Chairman
Scottish Medicines Consortium

Indication

Routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older [1]

Dosing Information

The recommended dose for adults and adolescents aged 12 years and older weighing ≥40kg is 150mg berotralstat orally once daily. It can be taken at any time of the day, with food. If a dose of berotralstat is missed, the patient should take the forgotten dose as soon as possible without exceeding one dose per day.[1]

Product availability date

September 2021

Berotralstat received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 30 October 2020. The indication was for the routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older.

Berotralstat meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Berotralstat inhibits plasma kallikrein, which is a serine protease that cleaves high-molecular-weight-kininogen (HMWK), releasing bradykinin, a potent vasodilator that increases vascular permeability. In patients with HAE due to C1-inhibitor deficiency or dysfunction, normal regulation of plasma kallikrein activity is impaired, leading to uncontrolled increases in plasma kallikrein activity and bradykinin release, resulting in HAE attacks.[1]

The submitting company requested that SMC considers berotralstat for use in patients who experience ≥ two clinically significant attacks per month.

The key evidence supporting the efficacy and safety of berotralstat comes from APeX-2, a randomised, double blind, international, placebo-controlled, three-part, phase III study in patients with HAE. This study recruited patients aged ≥12 with a clinical diagnosis of HAE type I or II and ≥ two HAE attacks that met all the protocol-defined requirements during the run-in period (of maximum 8 weeks from the screening visit). Patients were eligible if they had access to and ability to use one or more standard of care (SoC) treatment for acute attacks of HAE.

In APeX-2 part 1, patients were randomised equally to receive orally once daily: 110mg berotralstat (n=41; not a licensed dose; thus, it will not be considered further); 150mg berotralstat (n=40; licensed dose) or placebo (n=40) for 24 weeks. Randomisation was stratified according to the HAE attack rate at baseline (≥ two attacks per month versus< two attacks per month).[2,3] Patients continued to use their prescribed acute medication to treat any attacks. Prophylaxis of

HAE attacks with C1-esterase inhibitor, androgens or tranexamic acid was prohibited during the study.[3]

The primary efficacy outcome was the monthly rate of investigator-confirmed HAE attacks during the 24-week treatment period. Efficacy analyses were performed in the intent-to-treat (ITT) population, which included all randomised patients, regardless of whether study treatment was administered. The primary and three secondary outcomes were formally tested in a hierarchical fashion; no formal testing was performed after the first non-significant outcome in the hierarchy.[3]

Over the 24-week treatment period, berotralstat 150mg was associated with a statistically significant reduction in the rate of investigator-confirmed HAE attacks compared with placebo. Secondary outcomes showed numerical improvements with berotralstat 150mg versus placebo. Relevant primary and secondary outcomes results are detailed in Table 1 below, in the hierarchical order used.

Table 1: Primary and secondary outcomes results of APeX-2 part 1 (ITT population) [2]

	Berotralstat 150mg (N=40)	**Placebo (N=40)**
Primary outcome		
Estimated monthly investigator-confirmed attack rate over 24 weeks	1.31	2.35
Difference versus placebo (95% CI), p-value	-44% (-60 to -23), p<0.001	
Secondary outcomes		
Change from baseline in AE-QoL total score at week 24	-14.6	-9.7
LSM difference versus placebo (95% CI), p-value	-4.9 (-12.2 to 2.4), p=0.188	
LSM proportion of days patients had angioedema symptoms over 24 weeks	0.12	0.20
LSM difference versus placebo (95% CI)	-0.08 (-0.13 to -0.02)[a]	
Estimated monthly investigator-confirmed attack rate during dosing in the effective treatment period (Day 8 through 24 weeks)	1.27	2.38
Difference versus placebo (95% CI)	-47% (-62 to -26)[a]	

Notes: [a] Not formally tested due to a break in the hierarchical testing order.
Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire (angioedema-specific 17-item questionnaire, with scores ranging from 0 to 100; decreased score indicates an improvement in the patient's QoL; the minimum clinically important difference is -6); CI, confidence interval; ITT, intent to treat; LSM, least squares mean; N, number of patients.

Relevant to the proposed positioning, a pre-specified subgroup analysis of the primary efficacy outcome for baseline attack rate was conducted. In the subgroup of patients with ≥ two attacks/month (n=30 in berotralstat group and n=27 in placebo group), a similar decrease in the rate of investigator-confirmed attacks was seen: attack rate reduction of 40% with berotralstat versus placebo (1.76 and 2.92 attacks per month, respectively; p=0.005).[4]

In APeX-2 part 2, patients continued berotralstat the same dose as in part 1, or if initially randomised to placebo, they were re-randomised to berotralstat 150mg or 110mg from week 24 to 48.[3,5] One hundred and eight patients received one or more doses of berotralstat in part 2. The reduction in mean attack rate was improved between the end of the week 24 and the end of week 48. In patients who completed 48 weeks of dosing with berotralstat 150mg (n=31), mean HAE attack rate declined from 2.9 attacks per month at baseline to 1.5 attacks per month at month 6, and 1.0 attack per month at month 12.[6]

In APeX-2 part 3, patients received open-label berotralstat 150mg for up to 144 weeks (approximately 3 years).[3] Eighty-two patients continued onto the open-label part 3 during which all patients were transitioned to berotralstat 150mg at various timepoints. There was a sustained reduction in HAE attack rate per month across 96 weeks. In patients who completed 96 weeks of dosing (across the three study parts) with berotralstat 150mg (n=21), mean HAE attack rates declined from 2.8 attacks per month at baseline to 1.0 in month 6, 0.6 in month 12 and 0.3 in month 24.[7]

Summary of evidence on comparative safety

Berotralstat appears to have an acceptable safety profile. Most adverse events (AE) were mild to moderate in severity. The limited safety data means rare AEs may not have been identified.[2]

In the APeX-2 study part 1, any treatment-emergent AE was reported by 85% (34/40) of patients in the berotralstat group and 77% (30/39) in the placebo group and these were considered treatment-related in 38% and 33% respectively. In the berotralstat 150mg group and placebo groups respectively, patients with a reported serious AE were 0% versus 7.7% and patients discontinuing therapy due to an AE was 2.5% versus 2.6%.[2]

The most frequently reported treatment emergent AEs of any grade with an incidence >10% in the berotralstat 150mg group versus the placebo group were: upper respiratory tract infection (30% versus 28%), nausea (15% versus 18%), vomiting (15% versus 2.6%), diarrhoea (15% versus 0%), headache (10% versus 5.1%), abdominal pain (23% versus 10%), and back pain (10% versus 2.6%).[4]

*Other data were also assessed but remain confidential.**

Summary of clinical effectiveness issues

Hereditary angioedema (HAE) is a serious and potentially life-threatening genetic disease that is caused by mutations in the gene coding for C1-esterase inhibitor, resulting in deficiency or dysfunction of C1-inhibitor protein.[2] It is characterised by recurrent, acute attacks of angioedema in the skin, pharynx, larynx, gastrointestinal tract, genitals, and extremities, resulting in severe pain and disfigurement.[9] Treatment of HAE includes acute treatment of attacks and prophylactic treatment. All patients should be evaluated for long-term prophylaxis. Prophylactic treatment options include: attenuated androgens (such as stanozolol and danazol), anti-fibrinolytics (such as tranexamic acid), C1-esterase inhibitor (such as Cinryze®), and lanadelumab (SMC2206), which was

accepted by SMC for restricted use within NHSScotland for patients who would otherwise be considered for long-term prophylaxis treatment with C1-esterase inhibitor.[2,10]

Clinical experts consulted by SMC considered that berotralstat fills an unmet need in this therapeutic area and is a therapeutic advancement, which would provide an orally-administered option, for long-term prophylactic use. No service implications are anticipated. The submitting company requested that SMC considers berotralstat for use in patients who experience ≥ two clinically significant attacks per month.

Key strengths

- In adults and adolescent patients with HAE type I or II, berotralstat 150mg significantly reduced the monthly rate of HAE attacks by 44% compared with placebo over the 24-week treatment period.
- The evidence supports the submitting company's proposed positioning (experience ≥ two clinically significant attacks per month) as the majority of patients in APeX-2 had experienced ≥ two attacks per month.
- Data from APeX-2 parts 2 and 3 suggest that the effect of berotralstat is maintained through to 24 months of treatment.

Key uncertainties

- Improvements were seen with berotralstat 150mg compared with placebo also with the secondary outcomes, however the first hierarchically tested secondary outcome (Angioedema Quality of Life) was not statistically significant; therefore, all other secondary outcomes were not formally tested.
- The study sample size was small (only 40 patients were randomised to berotralstat 150mg and 40 to placebo) and very few patients completed 24 months of treatment (only 21 patients); thus, uncertainty remains around the long-term efficacy and safety of berotralstat.[5,7]
- There are limited data in adolescents (only four were included in both the berotralstat 150mg and placebo groups) and the elderly population (no patient was ≥75 years old). APeX-2 part 3 is ongoing and due to complete in September 2023.[11] To further characterise long-term safety, tolerability, and effectiveness of berotralstat in the real-world setting, including growth and development in adolescent patients, a post authorisation non-interventional safety study has been agreed.[2]
- Clinical experts consulted by SMC suggested that in clinical practice eligibility for prophylactic treatment is based on various factors including the frequency, severity, physical and quality of life impact of attacks and not solely on attack number.
- The submitting company considered that there are no relevant active comparator treatments in the proposed positioning for berotralstat, and that SoC without prophylactic treatment is the only relevant comparator. However, clinical experts consulted by SMC considered that that C1-esterase inhibitors, lanadelumab, attenuated androgens and

tranexamic acid were potentially relevant active comparators. Tranexamic acid and attenuated androgens are not licensed in this indication and C1-esterase inhibitors and lanadelumab are restricted to use in patients with a higher attack frequency than the company's proposed positioning.

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 **berotralstat**, as an **orphan equivalent medicine**, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- HAE is highly variable, from mild and infrequent to frequent, intrusive, painful and life threatening. The unpredictability of episodes and lifetime risk of life-threatening laryngeal oedema are for patients and their families a major source of anxiety and have a substantial impact on their quality of life.
- Despite the availability of prophylactic treatment options, some patients remain very symptomatic and there is an unmet need for safe, effective and easily administered prophylactic options.
- Berotralstat, as an effective and well-tolerated oral prophylaxis, would help address this need. It will offer an additional prophylactic option, allowing for an individualisation of treatment and for consideration of patients' preferences.
- In responders, berotralstat is expected to significantly reduce symptom burden and anxiety linked to the risk of acute attacks for both patients and their families. It would improve their quality of life and allow increased participation in work/education/family activities.
- Its convenient oral administration is a major advantage over parental prophylactic options. This will help reduce hospital visits for infusions. It will be preferred by patients who are needle phobic, or experience discomfort with parental administration, or have poor venous access.
- It may be better tolerated than some of the oral prophylactic options currently in use, particularly androgens.
- With regards to berotralstat positioning, PACE participants preferred a more flexible approach based on clinical judgment (e.g. with a wording referring to clinically significant disabling attacks) to use of cut-offs by number of attacks.

Additional Patient and Carer Involvement

We received a patient group submission from HAE UK, which is a registered charity. HAE UK has received 80% pharmaceutical company funding in the past two years, including from the submitting company. A representative from HAE UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis assessing berotralstat for the routine prevention of recurrent attack of HAE in adult and adolescent populations aged 12 years and older who experience ≥2 clinically significant attacks per month.

The comparator used in the base case was the standard of care, defined as avoidance of triggers known, or suspected, to cause HAE attacks, combined with treatment of acute attacks as they occur. Patients can receive either one, or a combination of four medicines, two of which were intravenous plasma-derived C1-esterase inhibitors (Berinert® or Cinryze®), one was an intravenous recombinant C1-esterase inhibitor (conestat alfa), and the other was a subcutaneous bradykinin receptor agonist (icatibant). Experts have advised that additional comparators of relevance include prophylactic treatment with C1-esterase inhibitors, lanadelumab (accepted for restricted use by SMC), attenuated androgens or tranexamic acid, which may be used more widely in clinical practice in Scotland. The model does not consider these. The submitting company notes there are current supply chain issues with attenuated androgens.

A two- state ('alive' or 'dead') Markov model was created whereby within the alive state patients could either be in an attack state or attack-free. Cycle length was 28 days and the model time horizon was the remaining lifetime of the patient. This was tested in scenario analysis, as was the average patient age at baseline (to account for adolescents receiving treatment from this age compared with the average age of patients seen in clinical practice).

Clinical data to inform the model came from APeX-2, and used data from the sub-set of patients with ≥2 attacks per month at baseline, as per the proposed positioning. Data were extrapolated beyond the study follow up period on the basis of last observation carried forward (LOCF) which assumes there is no treatment waning over the remaining lifetime of the patients. This assumption was tested in sensitivity analysis on request, as was the proportion of patients who met the definition of response (at least 50% or greater reduction in the number of attacks). The 3 month cut-off for continuation of treatment depending on whether or not a response was shown was tested, but the corresponding effect on background discontinuation of treatment (assumed to be zero in the base case) was not described.

Utility scores used in the base case model came from a study by Nordenfelt 2014 [12], which has been used in previous submissions to NICE for this condition[13]. The APeX-2 study had collected EQ-5D data but these were not used in the economic model. The submitting company's justification for not using the study data was that the data collection points for the EQ-5D may not necessarily correspond to the time at which a patient might be experiencing an attack, and therefore couldn't fully account for the extent of disutility associated with the condition. A scenario analysis considers alternative utility values obtained from a Time Trade Off (TTO) study commissioned by the submitting company (table 3 scenario 6).

Medicine acquisition costs for berotralstat and the four standard of care treatments for treating acute attacks were costed. The cost associated with standard of care treatment depended on what treatment combination was used (sometimes multiple doses were necessary). These data

were taken from APeX-2 and thus the treatment cost associated with an acute attack varied between the intervention and comparators in the model. Scenario analysis was provided assuming the same treatment was used for all patients experiencing an acute attack (table 3 scenarios 11 to 14).

Resource use associated with having an attack was quantified based on expert UK clinical consensus regarding the components involved and the proportions of patients incurring each resource. It therefore appears that each resource is incurred once. This seems fairly reasonable for the resource use items involved i.e. A&E visits (and hospitalisations), intubation, radiography, ambulance transport and blood tests. There may be some under-estimation (e.g. unit costs for blood tests) but it would be unlikely to alter the results considerably. Wastage costs apply to only one of the standard of care treatments and so were stated to have been ignored in the model.

A Patient Access Scheme (PAS) was proposed by the submitting 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. PAS discounts are also in place for conestat alfa and icatibant and these were included in the results used for decision-making by using estimates of the comparator PAS price. SMC is unable to present the results provided by the company that used an estimate of the PAS price for conestat alfa and icatibant due to commercial confidentiality and competition law issues. As such, the main economic results are shown in the tables below using list prices for all medicines.

Table 2: Base case results (list prices for all medicines):

Comparison	ICER (cost per QALY gained) (£)
Berotralstat versus SoC	£743,158

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality adjusted life years; SoC, standard of care.

Table 3: Scenario analyses (list prices for all medicines)

	Parameter	Base case	Scenario setting	ICER at list prices (all medicines)
1	Perspective	NHS and PSS	Societal	£478,099
2	Time horizon	Lifetime (58 years)	10 years	£790,955
3			20 years	£749,887
4	Age	42 years	12 years	£722,303
5	Continuation rule	Included	Excluded	£993,282
6	Source of patient utility values	Nordenfelt et al. (2014)	TTO study	£1,002,294
7	Administration disutilities	Excluded	Included	£562,602
8	Use of acute treatment	Unadjusted APeX-2 data	APeX-2 data adjusted by UK clinical opinion	£524,989
9	Treatment waning	Excluded	12% reduction in efficacy for every 5 years of the time horizon	£1,125,571
10	Standard of care treatment used	Unadjusted APeX-2 data	Berotralstat patients receive same treatment combinations as standard of care patients	£757,722

11	Standard of care treatment used	Unadjusted APeX-2 data	All treated with C1 esterase inhibitor (Berinert®)	£555,607
12	Standard of care treatment used	Unadjusted APeX-2 data	All treated with C1 esterase inhibitor (Cinryze®)	£996,915
13	Standard of care treatment used	Unadjusted APeX-2 data	All treated with conestat alfa	£671,871
14	Standard of care treatment used	Unadjusted APeX-2 data	All treated with icatibant	£746,887

Abbreviations: NHS, National Health Service; QALY, quality-adjusted life year; TTO, time trade-off.

The main limitations of the economic case are as follows:

- Using frequency of attacks within the positioning may be less relevant to Scotland where restricted use is not specifically dependent on a cut off relating to attack frequency.
- Using last observation carried forward from the study in the base case does not account for the possibility of treatment waning. The submitting company argued in response to Economic Assessor queries that treatment waning was unrealistic and the data suggest that treatment with berotralstat may improve over time. However, Table 3 includes the scenario analysis they provided that accounted for treatment waning of 12% reduction in efficacy for every 5 years of the time horizon (scenario 9).
- Published utilities data were used despite the collection of EQ-5D data in the study (although the base case source used has been used in previous submissions in this area). The submitting company provided an analysis on request using a cost-minimisation approach. This showed that the additional cost of berotralstat was £2,587,016 at list prices for all medicines.
- The submitting company provided a large list of combinations of standard of care therapies used to treat attacks. The model results were not sensitive to assuming berotralstat patients received the same combinations of treatments as the standard of care patients (i.e. assuming equivalence in the costs associated with treating an attack, table 3 scenario 10). However, the results did show variability when assuming that all attacks would be treated by the same standard of care treatment (scenarios 11 to 14), although the submitting company has pointed out that this scenario is considerably different to how treatment is expected to be provided within the NHS in Scotland.
- The model does not include all available comparator therapies used in clinical practice in Scotland, notably prophylactic C1-esterase inhibitors, lanadelumab, attenuated androgens and tranexamic acid. We would have liked to have seen at least one analysis that incorporates the possibility of these treatments that are used in clinical practice in Scotland.

The Committee considered the benefits of berotralstat in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as berotralstat is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted berotralstat for restricted use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The United Kingdom Primary Immunodeficiency Network and Hereditary Angioedema UK developed and published in 2015 a consensus document '*C1 inhibitor deficiency: 2014 United Kingdom consensus'*[10], an update from the first UK consensus document published in 2005.[14] The consensus statements makes the following relevant recommendations regarding the management of HAE:

- For acute treatment, acceptable treatments supported in this consensus statement include intravenous plasma-derived C1- inhibitors (such as Berinert®, Cinryze®), recombinant human C1-inhibitor (conestat alfa) or icatibant, a subcutaneous bradykinin-receptor antagonist.
- Regular prophylactic treatment with C1 inhibitor may be appropriate for patients requiring treatment for two or more attacks per week.
- The evidence for the efficacy of anti-fibrinolytic for long-term prophylaxis is acknowledged to be limited; however, a minority of patients may find them helpful.
- Attenuated androgens, are considered effective in long-term prophylaxis in most people and should be used at the lowest effective dose to minimize side effects (more than 200mg daily of danazol or more than 4mg daily of stanozolol should be exceptional).
- The use of attenuated androgens should be avoided in pre-adolescent children.
- Tranexamic acid is the drug of choice for prophylaxis in children.

In 2018, the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI) published the international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update.

This guidance recommends that:[15]

- HAE attacks are treated with either C1 esterase inhibitor, ecallantide, or icatibant.
- Prophylaxis should be considered for patients who face events in life that are associated with increased disease activity.
- Patients should be evaluated for long-term prophylaxis at every visit. Disease burden and patient preference should be taken into consideration.
- C1 esterase inhibitors are recommended for first line long-term prophylaxis.
- Androgens are suggested to be used as second-line long-term prophylaxis. However, they must

be regarded critically, especially in light of their side effects. The minimal effective dose should be used.

- There should be the adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimise burden of disease.
- In children, plasma-derived C1-inhibitor is the preferred therapy for long-term prophylaxis. When C1-inhibitor concentrate is not available for long-term prophylaxis, antifibrinolytics (that is tranexamic acid 20-40mg/kg) are preferred to androgens because of their better safety profile; however, efficacy is questioned, and data are not available supporting its use.

These guidelines predate the availability of lanadelumab.

Additional information: comparators

Standard of care.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Berotralstat	**150mg orally once daily**	**£132,665**

Costs from MIMS online. Costs do not take Patient Access Schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 7 patients receiving treatment in year 1 rising to 19 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73(8):1575-96.

This assessment is based on data submitted by the applicant company up to and including 10 December 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.