Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2206

lanadelumab 300mg solution for injection (Takhzyro®)

Shire, part of Takeda UK Ltd

8 November 2019

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 orphan equivalent process

lanadelumab (Takhzyro®) is accepted for restricted use within NHSScotland.

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

SMC restriction: patients with HAE type I or II, who would otherwise be considered for long-term prophylaxis treatment with C1-esterase inhibitor.

In a phase III study in patients with HAE, lanadelumab reduced the rate of angioedema attacks 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 list price that is equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Indication

For routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.[1]

Dosing Information

The recommended starting dose of lanadelumab is 300mg by subcutaneous injection every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300mg lanadelumab every 4 weeks may be considered, especially in patients with low weight. Lanadelumab is not intended for treatment of acute HAE attacks.

Lanadelumab should be initiated under the supervision of a physician experienced in the management of patients with HAE.[1]

Product availability date

Lanadelumab is expected to be launched in the UK in September 2019.
Lanadelumab meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Lanadelumab is a fully human IgG1 monoclonal antibody that inhibits plasma kallikrein proteolytic activity. Increased plasma kallikrein activity is known to cause angioedema attacks in patients with hereditary angioedema (HAE) through the production of cleaved high-molecular weight kininogen and bradykinin. The sustained regulation of plasma kallikrein activity by lanadelumab limits the production of bradykinin.[1] The submitting company has requested that SMC considers lanadelumab when positioned for use in patients with HAE type I or II, who would otherwise be considered for long-term prophylaxis treatment with C1-esterase inhibitor.

The evidence supporting the efficacy and safety of lanadelumab comes from HELP-03, a multicentre, randomised, double-blind, placebo-controlled, phase III study. The study comprised a 2-week screening, a 4-week run-in and 26-week double-blind treatment periods. Patients aged 12 years or older were required to have documented HAE type I or II, with a baseline attack rate of at least 1 attack every 4 weeks (as confirmed by investigators during a 4 week run-in period).[2]

Patients were randomised 2:1 to receive lanadelumab (n=84) or placebo (n=41) for 26 weeks in total, and patients in the lanadelumab group were further randomised 1:1:1 to receive either 300mg subcutaneously (SC) once every 2 weeks (n=27), 300mg SC once every 4 weeks (n=29), or 150mg SC once every 4 weeks (n=28). Patients in the placebo group received placebo SC injections once every 2 weeks (n=41). Patients receiving lanadelumab every 4 weeks received a placebo injection between active doses to maintain blinding. Since lanadelumab 150mg every 4 weeks is not a licensed dose, it will not be considered further. Randomisation was stratified according to the baseline attack rate observed during the 4-week run-in period (1 to <2, 2 to <3, and ≥3 attacks

per 4 weeks). Short-term prophylaxis treatment for HAE and treatment for acute HAE attacks was permitted; treatment choice was at the discretion of the investigator and could include intravenous C1 esterase inhibitor, icatibant, or ecallantide. The use of other long-term prophylaxis treatments was not permitted.[2, 3]

The primary outcome was number of investigator-confirmed HAE attacks during the 26-week treatment period. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients exposed to study treatment. Primary and key secondary outcomes were formally tested in a sequential manner; no formal testing of primary or key secondary outcomes was performed after the first non-significant outcome in the hierarchy.[2]

Over the 26-week treatment period, lanadelumab treatment groups were associated with statistically significant reductions in the mean number of investigator-confirmed HAE attacks compared with placebo. The model derived mean number of attacks per month from week 0 through week 26 was 0.26 in the 300mg once every 2 weeks group, 0.53 in the 300mg once every 4 weeks group, and 1.97 in the placebo group. There was a relative mean decrease of approximately 1.75 attacks/4 weeks in the 300mg once every 2 weeks groups, and 1.5 attacks/4 weeks in the 300mg once every 4 weeks treatment group compared with the placebo group.

Subgroup analysis results were broadly consistent with the main findings, although some subgroups may have been too small to detect differences between lanadelumab and placebo. The three key secondary outcomes of HELP-03 were met; lanadelumab was associated with a statistically significant reduction in number of attacks requiring acute treatment, number of moderate or severe attacks, and number of attacks occurring between week 2 and week 26 compared with placebo. Table 1 presents the results obtained from the primary and key secondary analyses.[2, 3]

Table 1. Primary and key secondary results - HELP-03 ITT population.[2, 3]

	Lanadelumab 300mg 2 weekly (n=27)	Lanadelumab 300mg 4 weekly (n=29)	Placebo (n=41)
Number of attacks per 4 weeks over 26 week treatment period			
Mean	0.26	0.53	1.97
Difference versus placebo (95% CI)	-1.71 (-2.09 to -1.33)	-1.44 (-1.84 to -1.04)	
Number of attacks requiring acute treatment per 4 weeks over 26 week treatment period			
Mean	0.21	0.42	1.64
Difference versus placebo (95% CI)	-1.43 (-1.78 to -1.07)	−1.21 (−1.58 to −0.85)	
Number of moderate or severe attacks per 4 weeks over 26 week treatment period			
Mean	0.20	0.32	1.22
Difference versus placebo (95% CI)	-1.01 (-1.32 to -0.71)	-0.89 (-1.20 to -0.58)	
Number of attacks occurring between week 2 and week 26 per 4 weeks			
Mean	0.22	0.49	1.99

Difference versus placebo (95% CI)	-1.77 (-2.16 to -1.38)	-1.50 (-1.91 to -1.09)	

CI = confidence interval, p<0.001 for all comparisons with placebo.

Exploratory, pre-specified responder analysis, found that 44% on lanadelumab 300mg once every 2 weeks and 31% on lanadelumab 300mg once every 4 weeks were attack-free for the 26 weeks treatment period compared with 2.4% in the placebo group.[3]

Health Related Quality of Life (HRQoL) was assessed using the Angioedema Quality of Life Questionnaire (AE-QoL). The questionnaire is self-administered, with scores ranging from 0 to 100. A lower score indicates lower impairment, and therefore greater quality of life. A difference in test score of 6 was deemed clinically meaningful. Across the 26-week treatment period, patients treated with lanadelumab experienced clinically meaningful improvements in AE-QoL over placebo. More patients in the 300mg once every 2 weeks group (81%), and 300mg once every 4 weeks group (63%) achieved the minimally clinically important difference in total quality of life score compared with placebo (37%).[2]

HELP-04 is an ongoing phase III, multicentre, open-label, long-term safety and efficacy study to evaluate lanadelumab in preventing acute angioedema attacks in patients with type I and II HAE. Patients who completed HELP-03 were eligible to "rollover" into this open-label extension study, in addition to "non-rollover" patients.[4,4] For patients who had previously been treated in HELP-03, the effect of lanadelumab on HAE attack rate was maintained. In the non-rollover patients, a treatment effect similar to patients in HELP-03 was observed, although non-rollover patients had a lower baseline attack rate compared with the rollover population.[5]

The submitting company presented Bayesian network meta analyses (NMAs) to indirectly compare lanadelumab with the intravenous C1 esterase inhibitor (Cinryze®) in patients aged ≥12 years with type I or II HAE. Two small studies, HELP-03 and CHANGE, were used to assess the outcome of attack rate (defined as the number of attacks per 28-day) which was used to inform the economic model.[2, 6]

Summary of evidence on comparative safety

In the HELP-03 study, any treatment-emergent adverse events (AE) were reported by 96% (26/27) in the 300mg 2 weekly group (n=27), 86% (25/29) of patients in the lanadelumab 300mg 4 weekly group, and 76% (31/41) in the placebo group. In the lanadelumab 300mg 2 weekly, lanadelumab 300mg 4 weekly, and placebo groups respectively, the proportion of patients with an AE felt to be treatment related by the investigator were 70%, 48%, and 34%; the proportion of patients with any reported serious AE were 3.7%, 10%, and 0%; the proportion of patients discontinuing therapy due to an AE was 0%, 3.4%, and 2.4%. No serious AEs were reported as treatment related throughout the study.[3]

The most frequently reported AEs of any grade with a incidence ≥5% in the lanadelumab 300mg 2 weekly, lanadelumab 300mg 4 weekly, and placebo groups were: injection site pain (52%, 31%,

and 29%), viral upper respiratory tract infection (37%, 24%, and 27%), headache (33%, 17%, 20%), injection site erythema (7.4%, 6.9%, 2.4%), injection site bruising (3.7%, 6.9%, and 0%), and dizziness (3.7%, 10%, and 0%). As headache and viral upper respiratory tract infection rates between lanadelumab groups and placebo were comparable, the most common AE felt to be treatment related was injection site reaction.[3]

Interim analysis of the open-label extension study, HELP-04, indicates that incidence rates for treatment emergent AEs are not increasing over time, and no further AEs have been identified with prolonged exposure. The EMA recognises that there is a lack of long-term safety data, but are satisfied that further data can be captured post-market authorisation.[3]

Summary of clinical effectiveness issues

Hereditary angioedema (HAE) is a rare autosomal dominant disorder that affects the gene responsible for producing C1 esterase inhibitor, resulting in deficiency (HAE type I) or dysfunction (HAE type II) of C1 esterase inhibitor protein. HAE is characterised by recurrent, acute attacks of angioedema which can commonly cause swelling of the face, larynx, gastrointestinal (GI) tract, limbs, and/or genitalia. Attacks are unpredictable, with most patients suffering multiple attacks annually and at multiple sites. Abdominal attacks can be disruptive and painful, whilst laryngeal attacks can restrict airways and are potentially life-threatening.

All patients with confirmed, severely symptomatic HAE (type I and II) should be considered for long-term prophylaxis, taking into account issues such as frequency of attacks, quality of life, patient decision, and failure to achieve adequate control by appropriate on-demand therapy. Long-term prophylactic treatments include, androgens such as stanozolol and danazol, and antifibrinolytics such as tranexamic acid, with plasma derived C1 esterase inhibitors such as Cinryze® or Berinert® (off-label) reserved for patients with more severe disease. Despite long-term prophylaxis, patients can still experience acute attacks and should also have on-demand medication prescribed. Lanadelumab for this indication meets SMC orphan criteria.[3, 7]

The submitting company has requested that SMC considers lanadelumab when positioned for use in patients, with HAE type I or II, who would otherwise be considered for long-term prophylaxis treatment with C1 esterase inhibitor.

The key study, HELP-03, met the primary outcome, with statistically significant reductions in the mean number of HAE attacks in 26 weeks, for lanadelumab treatment groups compared with placebo. Of particular note was the licensed starting dose of 300mg once every 2 weeks treatment group; a reported approximate mean decrease of 1.75 attacks every 4 four weeks. These findings can be considered both statistically significant and clinically meaningful. Additionally, lanadelumab met all three key secondary outcomes. The primary outcome of HELP-03 was an appropriate outcome for HAE, given the high mortality rate, unpredictability, and discomfort associated with HAE attacks. Secondary outcomes were not fully independent of the primary outcome however, which introduces a degree of redundancy to the results.[3]

There were some limitations with the key HELP-03 study. Given that HAE is a chronic condition that requires long-term management, the study duration of 26 weeks is a limitation, and consequently conclusions cannot be drawn on the long-term efficacy and safety of lanadelumab from the HELP-03 study alone. The open-label, non-comparative extension study, HELP-04, is ongoing and will provide longer-term safety and efficacy data; early interim data from HELP-04 appear to be consistent with the results of HELP-03. The EMA recognises that there is a lack of long-term data, but are satisfied that further data can be captured post-market authorisation.[2, 5]

There were some important differences in baseline characteristics between patients in the treatment groups of HELP-03, likely attributable to the small overall sample size. These included differences in sex, race, mean body mass index (BMI), and past medical history of HAE attacks. The differences in sex were particularly noteworthy, as it has previously been postulated in publications that disease severity is greater in women. There were fewer female patients in the lanadelumab groups compared with the placebo group (64% versus 83%), and this difference was particularly pronounced in the 300mg once every two weeks treatment group, which was only 56% female. However, subgroup analysis found no difference in attack rates between males and females, suggesting that the imbalance did not affect the overall results.[3]

UK consensus guidelines recommend that C1 esterase inhibitors should be used exceptionally for long-term prophylaxis when other means have not been effective. Consequently, patients who are considered for C1 esterase treatment (and therefore lanadelumab) in Scotland would likely have more severe disease (higher frequency of attacks) than the patients enrolled in HELP-03.[7]

There is no direct evidence comparing lanadelumab with C1 esterase inhibitors, which are considered the most relevant comparator in Scottish practice. This was addressed through the use of NMAs, which had several important limitations. Firstly, the NMA population was broader than the company's proposed population. Secondly, there was significant clinical and methodological heterogeneity between the two studies in the network. HELP-03 was a parallel group study which differed from CHANGE, which utilised a crossover study design. Treatment durations and assessment timepoints also varied; patients in HELP-03 were exposed to treatment for 26 weeks compared to 12 weeks in CHANGE (with an additional 12 weeks on placebo). Certain patient characteristics such as sex and prior prophylactic treatment varied markedly between treatment groups; the number of female patients in treatment groups ranged from 56% to 100%, and the number of patients with prior prophylactic treatment ranged from 9.1% to 69%. Furthermore, the eligibility criteria for each study differed; in the HELP-03 study to be eligible patients had to have ≥1 investigator confirmed HAE attack per 4 weeks. In the CHANGE study to be eligible for enrolment in the prophylactic study, patients had to have ≥2 HAE attacks per month. There were also issues with the interventions; CHANGE permitted patients to continue other prophylactic treatments including androgens and antifibrinolytics, which HELP-03 did not. The fixed dose 1000 International Units every 3 or 4 days of Cinryze® may not be reflective of clinical practice, as the SPC and clinical experts consulted by SMC have indicated that higher doses are commonly administered to achieve optimal control. Consequently, the efficacy seen in practice of Cinryze® may be greater than what is reported in CHANGE. Lastly, the analyses did not assess long term

efficacy, safety and health-related quality of life, which may be clinically relevant when considering the risk/benefit of treatments. Overall, given the limitations discussed, there is uncertainty in the reported results of the NMAs and no firm conclusions can be drawn.

Clinical experts consulted by SMC considered that lanadelumab is a therapeutic advancement due to positive clinical trial data and a favourable method of administration. There are potential benefits for both patient and service with the introduction of lanadelumab. The most relevant comparator (C1 esterase inhibitor) is an intravenous, blood product that requires two administrations per week. A proportion of these patients cannot self-administer at home and require hospital appointments for administration. Furthermore, blood products have a theoretical risk of blood borne virus transmission, which requires additional monitoring. There have also been concerns regarding the availability of blood products such as C1 esterase inhibitors in the UK, which could potentially leave patients without treatment if stock were to become unavailable. Lanadelumab is a subcutaneous injection, which can be administered every two weeks or every four weeks in patients with well controlled disease. The method and frequency of administration is more convenient for patients and is anticipated to reduce pressure on hospital based specialist services. Lanadelumab is only licensed for routine prevention of recurrent attacks of HAE. It is not licensed to treat acute attacks or for short-term prophylaxis in patients undergoing procedures.

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 lanadelumab, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- HAE is a disabling, potentially life-threatening, lifelong condition where patients can suffer frequent disabling acute angioedema attacks despite current treatments. The unpredictability of the acute attacks is a major source of anxiety for patients with HAE, and regularly interferes with daily life.
- There is an unmet need in this setting as the only C1 esterase inhibitor preparation licensed for prophylactic treatment has limitations: twice weekly intravenous infusions are cumbersome or even infeasible for some patients, and it is a blood based product and therefore associated with a small, theoretical risk of blood borne virus transmission. In addition, plasma-derived C1 esterase inhibitors are increasingly at risk of unpredictable worldwide shortages, which may leave patients without a prophylactic treatment.
- With a novel mechanism of action, lanadelumab is able to control angioedema with the opportunity for some patients to become attack-free and offers a potentially life-changing therapy.
- Lanadelumab would simplify treatment for patients with HAE. Administration is less frequent (once every 2 weeks, or once every 4 weeks in well-controlled patients), and has a less invasive

route of administration. After training, subcutaneous injections can be administered at home by patients which would reduce the amount of time spent in hospital for regular prophylactic therapy and/or acute rescue treatment for angioedema. This is seen as beneficial for both the patient and the service.

- Whilst results from studies are promising, it was acknowledged that durability of treatment response and long-term safety are unknown at this stage.
- The aforementioned benefits of lanadelumab would have a positive impact on quality of life for patients, family members and carers. Better control of attacks would enable patients to be more independent, remain in work or education, and fulfil their own parental and other caring responsibilities.

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 evaluating lanadelumab for routine prevention of recurrent attacks of HAE in patients aged 12 years and older, with a restriction to patients who would otherwise be considered for long-term prophylaxis treatment with C1 esterase inhibitor. Lanadelumab was compared with a blended comparator of C1 esterase inhibitor representing estimated usage of both Berinert® (off-label) and Cinryze®.

The submitting company selected a cohort-level Markov model comprised of two health states: “alive (with HAE)” or “dead”. The “alive” state was sub-divided into the proportion of patients anticipated to be attack-free (“attack-free period”), versus those likely to be experiencing an attack (“attack period”). Poisson regression analysis was used to estimate the average number of attacks per cycle, which determined the relative proportion of “attack-free” vs “attack period” patients at each cycle for landelumab. A lifetime time horizon was applied.

A Poisson regression analysis described above was conducted to derive per-cycle attack risk for lanadelumab. The Bayesian network meta-analysis described above was used to estimate attack rates only for the C1 esterase inhibitor comparator based on clinical data for Cinryze® ; in the absence of clinical data, Berinert® was assumed to be clinically equivalent to Cinryze® . Longer term estimates of attack rates were derived from the HELP-03 study (day 70 onwards), and a rate ratio was applied to derive event rates for C1 esterase inhibitor. Scottish general population mortality rates were applied. Treatment discontinuation rates from HELP-03 were used for patients treated with lanadelumab (who were assumed to subsequently receive C1 esterase inhibitor, whilst no treatment discontinuation was assumed for the comparator).

Utility estimates were applied based on an observational study and valued using the standard -5L to -3L 'crosswalk' method.[8, 9] As well as using a standard approach to estimate 'attack-free' utilities (0.825), this study amended the EQ-5D questionnaire to estimate utilities for the most recent attack experienced by patients (mild: -0.07; moderate: -0.369; severe: -0.486).

Medicine acquisition costs for both long term prophylaxis and acute treatments, administration costs, and management of select adverse events (liver enzymes and chest discomfort) were included. 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. The comparator cost represented an average of the acquisition costs of fixed dose Cinryze® and weight-based Berinert® dose, weighted based on hospital audit data from 2018 evaluating prescription patterns in the treatment of hereditary angioedema across Scotland. Dosing frequency was assumed to be the average duration reported within the Cinryze® summary of product characteristics (3.5 days). Dosing frequency for lanadelumab was assumed to reduce to once every 4 weeks for the majority of patients after six months, based on the proportion of patients who were attack-free at this point in HELP-03. Additional costs of training patients to self-administer were assumed for both treatments, and costs of managing acute attacks were included based on the management protocol within HELP-03 (for lanadelumab) and assumed Scottish clinical practice (for C1 esterase inhibitors).

The base case incremental cost-effectiveness ratios (ICERs) with the PAS are shown in the table below. The majority of changes in incremental costs were due to either the costs of long term prophylaxis or treatment of attacks, while the majority of quality adjusted life years (QALY) gains result from additional time spent attack-free, as well as benefits of subcutaneous versus IV administration.

Table 2: Base case results (with PAS)

Technologies	**ICER (£)**
C1 esterase inhibitor	Dominant
Lanadelumab	

ICER: Incremental cost-effectiveness ratio;

The company also provided a number of scenario analyses and others upon request. Scenarios of particular importance are summarised in table 3 below but all show that the result remained dominant (lanadelumab cheaper and more effective).

Table 3: Scenario analyses (with PAS)

	Description	ICER
1	Use of NMA results for both intervention & comparator	Dominant
2	58.5% of patients de-escalating to 300mg once per four weeks (based on log-normal extrapolation)	Dominant
3	Consistent management of acute attacks	Dominant
4	C1 esterase inhibitor discontinuation assumed equal to lanadelumab	Dominant
5	C1 esterase inhibitor dosing frequency of once every 4 days	Dominant
6	Use of fixed dose for Berinert® (1,000 IU)	Dominant
7	Pairwise comparison with Berinert® (20 IU/kg)	Dominant
8	Pairwise comparison with Cinryze® (1,000 IU)	Dominant
9	Shortened (ten year) time horizon	Dominant
10	Combined scenario: - Amended proportion of patients receiving Berinert® (67%) vs Cinryze® (33%) PLUS - Scenarios 1 - 4	Dominant
11	Combined scenario B: as per sensitivity analysis 10, with pairwise comparison to Berinert® (20 IU/kg)	Dominant

Inc: Incremental; QALYs: NMA: Network meta-analysis; IU: International units; NR: Not reported

An additional threshold analysis evaluating the influence of an average fixed dose of Berinert® highlighted that the ICER rapidly declines as the Berinert® dose increases, and applying base case assumptions with an average Berinert® dose of >1528 international units (when wastage is considered) is likely to result in dominant ICERs for lanadelumab.

The main limitations are as follows:

- Uncertainty exists in the appropriate dose/dosing frequency for both Cinryze® (use of an average 3.5 day dosing schedule) and Berinert® (weight-based vs fixed). The assumptions regarding relative proportions of comparators and dose of each (which ultimately determine the cost) are the main driver of the model. SMC clinical expert input suggests usage varies, although the proportions receiving Berinert may be within the range modelled by the company. However, sensitivity analysis demonstrated that the result remained dominant in scenarios testing alternative dosing and frequency assumptions.
- A high proportion of patients are assumed to reduce to the lower lanadelumab dosing frequency

by 12 months, based on data observed within the HELP-03 controlled clinical trial. Treatment in clinical practice may not result in as high a proportion of patients on the 4-weekly dosing schedule, which would result in a significant increase in incremental costs of lanadelumab. However, use of more conservative estimates in isolation do not alter the direction of the results (lanadelumab remains dominant).

- No randomised evidence is available for Berinert®, the predominant formulation of C1 esterase inhibitor applied within the base case, and an assumption of clinical equivalence to Cinryze® is applied.
- Due to the lack of direct comparative data, an NMA was used and subject to important limitations, as described in the clinical effectiveness section.
- Additionally, inconsistent approaches were taken to modelling the lanadelumab attack rate data (directly from a Poisson regression analysis) and comparator C1 esterase inhibitor data (indirectly applying a risk ratio to the placebo Poisson regression model). An alternative scenario was obtained where NMA results were utilised consistently for both the intervention and comparator. Although a small change in the results was observed, lanadelumab remained dominant.

The Committee considered the benefits of lanadelumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as lanadelumab 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, the Committee accepted lanadelumab for restricted use in NHSScotland.

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

Additional information: guidelines and protocols

A multi-disciplinary UK consensus statement on C1 esterase inhibitor deficiency was originally published in 2005 and was subsequently updated in 2009 and again in 2014; the current revised guidance was published in 2014.[7] This consensus statement makes the following relevant recommendations:

- Plasma-derived C1 esterase inhibitors (Berinert®, Cinryze®), recombinant C1 esterase inhibitor (Ruconest®) and Icatibant (Firazyr®) are all acceptable options for acute treatment
- Icatibant may be particularly useful in enabling self-administration as intravenous access is not necessary
- Regular prophylactic treatment with C1 esterase inhibitor may be appropriate for patients requiring treatment for two or more attacks per week
- Evidence for the efficacy of anti-fibrinolytics is poor; however, a minority of patients may find them helpful
- Attenuated androgens are effective in long-term prophylaxis for most people
- The lowest effective dose of attenuated androgen should be used to minimize side effects

- High doses of androgens may provoke severe side effects without added benefits
- Doses of danazol above 200mg daily should be exceptional
- Doses of stanozolol above 4mg daily should be exceptional
- Exceptionally, C1 esterase inhibitor prophylaxis may be required when control of acute attacks is not possible by other means (including for children). This should be reviewed at regular intervals.[7]

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.[10] This guidance recommends that:

- 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 should be used for first line long term prophylaxis
- Androgens should be used as second-line long-term prophylaxis
- There should be the adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease.[10]

Additional information: comparators

C1 esterase inhibitor (IV Cinryze®)

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Lanadelumab	**300mg SC once every 2 weeks***	**£322,920**
Cinryze®	1000 International Units IV every 3 or 4 days**	Every 3 days = £162,101 Every 4 days = £121,576

**Taken from the SPC: "In patients who are stably attack free on treatment, a dose reduction of 300mg lanadelumab every 4 weeks may be considered, especially in patients with low weight."*
***Recommended starting dose for routine prevention against angioedema attacks; the dosing interval may need to be adjusted according to individual response.*
Doses are for general comparison and do not imply therapeutic equivalence. Costs from company submission/BNF online on 29 July 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact and estimates of patient numbers 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.

SMC clinical expert responses indicate the number of patients eligible for treatment is likely to be higher than estimated by the submitting company.

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

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This assessment is based on data submitted by the applicant company up to and including 18 September 2019.

**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.