NICE National Institute for Health and Care Excellence

NICE guidance

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over

Technology appraisal guidance
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www.nice.org.uk/guidance/ta1101

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Garadacimab can be used as an option to prevent recurrent attacks of hereditary angioedema in people 12 years and over, only if:

- they have 2 or more attacks a month, and
- the company provides garadacimab according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with garadacimab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

What this means in practice

Garadacimab must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Garadacimab must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that garadacimab provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

Usual treatment for recurrent attacks of hereditary angioedema in people 12 years and over is long-term preventive treatment with berotralstat, C1-esterase inhibitors (C1-INHs)

or lanadelumab.

Clinical trial evidence shows that garadacimab reduces the number of hereditary angioedema attacks and increases the likelihood of freedom from attacks compared with placebo. Indirect comparisons suggest that garadacimab's clinical effectiveness is the same or better than berotralstat, C1-INHs or lanadelumab.

The most likely cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. So, garadacimab can be used as an option to prevent recurrent attacks of hereditary angioedema in people 12 years and over having 2 or more attacks a month.

2 Information about garadacimab

Marketing authorisation indication

2.1 Garadacimab (Andembry, CSL Behring) is indicated for the 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for garadacimab.

Price

2.3 The list price of garadacimab for the subcutaneous injection is £20,625 for each prefilled pen (200 mg/1.2 ml).

2.4 The company has a commercial arrangement. This makes garadacimab available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on CSL Behring's webpage on sustainability.

3 Committee discussion

The evaluation committee considered evidence submitted by CSL Behring, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Unmet need

Details of the condition

3.1 Hereditary angioedema is a rare genetic disorder. It is almost always caused by a mutation affecting the C1-esterase inhibitor (C1-INH) gene, known as type 1 or type 2 hereditary angioedema. Hereditary angioedema affects at least 1 in 59,000 people in the UK and usually develops between ages 8 and 12 years. It is a chronic condition involving recurrent unpredictable attacks of swelling in areas of the skin and submucosal tissue. The swelling may happen in the fingers and toes, face, mouth, abdomen, genitalia, gut or airway, and can cause severe pain. Swelling of the airway (laryngeal attacks) can be life threatening. The patient and clinical experts explained that swelling develops quickly over a few hours, but can take days or up to a week to go. After an attack, people feel drained, and have flu-like symptoms and extreme fatigue. Commenting on the draft guidance, Hereditary Angioedema UK emphasised that every person with hereditary angioedema is different. Additional treatment options are important because existing treatment options do not suit everyone with the condition.

The clinical experts explained that attacks should be treated with on-demand treatment as soon they happen. They advised that the aim of preventive treatment is to reduce the number and severity of attacks. The patient and clinical experts emphasised that people with hereditary angioedema particularly value freedom from attacks. This is because of the severe anxiety caused by anticipating future attacks, which diminishes with time since the last attack. They advised that, although people on existing treatments could have no attacks, breakthrough attacks can occur because hereditary angioedema is very unpredictable. These are often caused by stressful life events, such as exams, surgery, a car crash, bereavement or giving birth. Attacks may become more

pronounced when there are changes in hormone levels, particularly oestrogen, during puberty and menopause. People can also have long periods with more frequent or more severe attacks, which have a significant impact on quality of life and are associated with extreme anxiety. Hereditary angioedema can disrupt education and affect the choice of college, university and career, and can also make travelling for work and leisure extremely challenging. They noted the impact in young people (aged 12 to 17 years) and explained that painful abdominal or facial attacks can lead to stigma and stop people from going out.

The committee recognised that hereditary angioedema can be severe and debilitating, and the unpredictability of attacks causes considerable anticipatory anxiety for people with the condition. It understood that the condition varies greatly between different people, so treatment is highly individualised. It also noted that people with well-controlled attacks can still have breakthrough attacks and these are a significant source of worry. The committee concluded that there is an unmet need for additional effective treatment options to prevent recurrent attacks of hereditary angioedema.

Clinical management

Preventive treatment options

3.2 In NHS England's algorithm of commissioned treatment options for hereditary and acquired angioedema secondary to C1-INH deficiency (PDF only) eligibility for long-term preventive treatment is defined by attack frequency:

- People having 2 or more attacks a week despite oral treatments can have:
  - lanadelumab, which is given as a subcutaneous injection every 2 to 4 weeks and can be used by people 2 years and over, or
  - human-plasma-derived C1-INHs, which are given by slow intravenous injection or infusion every few days or weekly, and can be used by all ages.
- People having 2 or more attacks a month can have berotralstat. This is a daily oral treatment that can be used by people 12 years and over.

- People having fewer than 2 attacks a month can have on-demand treatment only.

  The company presented evidence from a panel of 59 UK healthcare professionals, which reported that eligibility criteria for preventive treatment based only on attack frequency are too simplistic. It also reported that the criteria disadvantage people who would benefit substantially from long-term preventive treatment but are unable to access it because they do not meet the attack frequency criteria. Stakeholder submissions stated that children and young people are likely to have a lower attack frequency than adults. So, they may not meet the attack frequency criteria for preventive treatments but can still be significantly affected by the condition. The submission from Hereditary Angioedema UK noted that severity of attacks, which can vary, is not captured in eligibility criteria for preventive treatment. The committee noted that some people have difficulty swallowing tablets, so alternatives to oral treatment are valuable. It noted that garadacimab is a self-injected treatment that can be kept at room temperature for up to 2 months. This gives people with the condition more flexibility to travel with a medicine for their condition and more freedom of choice. The committee concluded that people with hereditary angioedema and healthcare professionals would welcome an additional preventive treatment option to improve treatment choice.

Positioning of garadacimab

3.3 The company submission positioned garadacimab as an alternative to berotralstat, C1-INHs or lanadelumab for hereditary angioedema in people 12 years and over having 2 or more attacks a month. At technical engagement, the company clarified that the comparator being modelled differed by attack frequency:

- berotralstat was modelled for people having 2 or more attacks a month
- C1-INHs and lanadelumab were modelled for people having 2 or more attacks a week.

The EAG agreed with this overall positioning of garadacimab and the comparators. It also suggested that line of treatment should be explored for people having 2 or more attacks a month when alternative preventive options are most needed. This is because berotralstat is the only preventive treatment option. The EAG explored positioning garadacimab as a first-line option instead of berotralstat or as a second-line option after berotralstat compared with no preventive treatment.

The company noted throughout the evaluation that 'no preventive treatment' was not a comparator in the final scope. It suggested that people having garadacimab at first line would not have berotralstat at second line. The EAG explained that considering garadacimab after berotralstat was consistent with the NHS England treatment algorithm. In this algorithm, lanadelumab is available for people having 2 or more attacks a week despite oral treatments (mainly berotralstat). The EAG's clinical experts explained that people might switch their first-line treatment between berotralstat and garadacimab because of side effects or lack of efficacy. The EAG explained that there was limited data for people continuing berotralstat after 3 months. So, it thought that the indirect comparison with berotralstat was highly uncertain (see section 3.10 and section 3.11). It noted that, in the VANGUARD trial, garadacimab was compared with placebo. So, comparing garadacimab with no preventive treatment in the model provided a more certain direct comparison. The EAG explained that berotralstat had been shown to be cost effective compared with best supportive care (with no preventive treatment) in NICE's technology appraisal guidance on berotralstat for preventing recurrent attacks of hereditary angioedema (from here, TA738). So, if garadacimab also showed cost effectiveness compared with no preventive treatment, this could reduce the uncertainty about the indirect comparison of garadacimab and berotralstat (see section 3.6).

The committee understood that, in UK clinical practice, berotralstat is stopped if the number of attacks each month does not reduce by at least 50% after 3 months. Because berotralstat does not work well for everyone, there is a particular need for an alternative treatment option for people having 2 or more attacks a month (compared with 2 attacks a week, for which there are more available treatments). So, the committee decided that exploring second-line garadacimab compared with no preventive treatment

was reasonable. The clinical experts at the first committee meeting advised that, if both berotralstat and garadacimab were available, they would often suggest trying berotralstat first because many people prefer an oral treatment. Stakeholders commenting on the draft guidance and the patient and clinical experts at the second meeting noted that they would prefer to have both treatment options available for people having 2 attacks or more a month. They also said that decision making on choice of treatment would involve the people with the condition. The committee noted that some people have difficulty swallowing tablets, so may prefer less frequent self-injected medicines. The committee concluded that the company's overall positioning of garadacimab and its comparators, which were determined by attack frequency, was appropriate. It concluded that it would consider cost effectiveness separately in people having 2 or more attacks a week and 2 or more attacks a month.

Clinical effectiveness

VANGUARD trial

3.4 The clinical-effectiveness evidence for garadacimab was from VANGUARD. This was a phase 3, randomised, double-blind, placebo-controlled trial. It compared garadacimab (200 mg by subcutaneous injection every 4 weeks) with placebo in 64 people 12 years and over with type 1 or 2 hereditary angioedema. Participants could not use any other preventive treatment during the trial. The intention-to-treat population had 1 or more attack a month over the run-in period of the trial. The primary outcome was the time-normalised number of hereditary angioedema attacks during the 6-month treatment period. The committee noted that the trial was small and did not include people in the UK. The EAG noted the eligibility criteria of 3 or more attacks during the 3 months before screening, which was not specified in the NICE scope. The committee recalled that the company's positioning of garadacimab was for people having more frequent attacks (2 or more a month). The clinical experts noted that there was no experience of using garadacimab in the UK. So, there was uncertainty about how it compared with other preventive treatments used in UK clinical practice. The committee concluded that the trial results were likely to be generalisable to people in the UK

having recurrent attacks of hereditary angioedema. But this was associated with some uncertainty because people in the trial had a lower minimum frequency of attacks than people who might be eligible for garadacimab in UK clinical practice.

Clinical-effectiveness results

3.5 The mean age in VANGUARD was 41 years and almost 60% of participants had a history of laryngeal attacks. In the 3 months before screening, attacks most commonly occurred in the abdomen and extremities (hands and feet). The mean number of hereditary angioedema attacks during the 6-month treatment period was 0.3 a month with garadacimab compared with 2.0 a month with placebo. This was equivalent to an 86.5% reduction in mean number of attacks each month with garadacimab. During the trial, 61.5% of people in the garadacimab arm had no attacks compared with 0% in the placebo arm. Garadacimab reduced the mean number of moderate or severe hereditary angioedema attacks each month by 90% compared with placebo. The company reported a post-hoc analysis of longer-term effectiveness from pooled results from VANGUARD and an open-label phase 3 study. It noted that the efficacy of garadacimab in reducing the time-normalised number of attacks from baseline was maintained beyond the randomised 6-month treatment period of VANGUARD. There was also no evidence of a waning of treatment effect after more than 2 years of treatment. The company suggested that this reduced the uncertainty associated with the relatively short treatment period in VANGUARD. The committee noted that it would have liked to have seen results from a phase 3 trial that compared garadacimab with standard-care treatments. It concluded that the clinical evidence suggested that garadacimab was more effective than placebo at reducing the number of hereditary angioedema attacks.

Indirect treatment comparison

3.6 Because of the lack of direct evidence comparing garadacimab with berotralstat, C1-INHs or lanadelumab, the company did indirect treatment comparisons. Its preferred approach was a fixed-effect network meta-analysis (NMA) of trials in people 12 years and over with hereditary angioedema. After technical engagement, the company and EAG both preferred the NMA of phase 3 placebo-

controlled trials of garadacimab (VANGUARD), berotralstat (APeX-2 and APeX-J), lanadelumab (HELP-03, with every 2 week and every 4 week dosing) and the C1-INH Berinert (COMPACT). The company considered the treatment effect estimates produced by the NMA to be confidential, so they cannot be reported here. The committee noted that it had reviewed the NMA results, which were presented for several hereditary angioedema efficacy outcomes and for adverse events. It noted that time-normalised number of attacks was the key efficacy outcome used in the company's model (see section 3.7). It was also aware of a similar fixed-effect NMA that included the phase 2 and phase 3 trials of garadacimab, which was published by Walsh et al. (2025). This showed that garadacimab was similarly effective to lanadelumab every 2 weeks and subcutaneous C1-INH, and more effective than berotralstat, in reducing the rate of time-normalised number of hereditary angioedema attacks. The committee concluded that the treatment effect estimates provided in the company's fixed-effect NMA of phase 3 trials were suitable for decision making. It also concluded that garadacimab has similar or better clinical effectiveness compared with berotralstat, C1-INHs or lanadelumab.

Economic model

Company's model structure

3.7 The company submitted a cohort-based Markov model. It had 3 primary health states (alive with an attack, alive without an attack and dead) with 6 tunnel states for the number of months without attacks. Hereditary angioedema attack severity could be mild, moderate, severe non-laryngeal or severe laryngeal. The company explained that severe non-laryngeal or severe laryngeal attacks were modelled separately because of differences in resource use. Cycle length was 28 days without half-cycle correction and the model had a lifetime horizon (60 years). For each treatment in the model, the rate ratio of time-normalised number of hereditary angioedema attacks from the indirect treatment comparison was applied to the mean number of attacks each month from the VANGUARD placebo arm. This modelled the number of attacks each cycle for each treatment. Background mortality for use within the economic model was based on UK life tables from the Office of National Statistics (2024). Disease-specific mortality

was not considered for garadacimab or comparators in the model. Both costs and outcomes were discounted at 3.5% annually, as for the NICE reference case. The EAG agreed with the company's overall approach, except for the inclusion of tunnel states in the 'alive without an attack' health state. This was because, in VANGUARD, the most significant impact on health-related quality of life occurred within the first month of treatment. So, monthly tunnel states are unlikely to be needed to capture health-related quality-of-life improvements after an attack (see section 3.13). At the second committee meeting, the company aligned with the EAG by removing the tunnel states. The committee concluded that the company's model structure without using tunnel states was acceptable for decision making.

Baseline attack frequency

3.8 At the second committee meeting, the company noted that the baseline attack frequency in the trial was lower than that assumed in TA738 (3.1 attacks a month based on APeX 2) and that seen in people included in cohort 2 of the berotralstat real-world evidence audit (data is confidential; see section 3.11). The company proposed that scenario analyses should be considered for baseline attack frequency. The EAG explained that the economic model was highly sensitive to baseline attack frequency, and that a higher frequency was favourable to garadacimab. The EAG thought that the berotralstat audit data was the best source of evidence on baseline frequency. This was because it was a UK real-world study, so was more likely to be representative of UK clinical practice than a trial. But it disagreed with the company that analysis of this should be limited to the cohort of people whose condition responded to berotralstat. The EAG thought that it was more appropriate in its model to use the baseline attack frequency from the intention-to-treat population of the berotralstat audit for people having 2 or more attacks a month at baseline and who started treatment after the positive reimbursement decision for berotralstat. This led to a large improvement in the incremental cost-effectiveness ratio (ICER) for garadacimab compared with berotralstat. At the second committee meeting, the company aligned with the EAG's updated baseline attack frequency in its model. The committee agreed that this was most likely to be representative of UK clinical practice. It concluded that the updated baseline attack frequency modelled by the company and EAG was appropriate for decision making.

Treatment effectiveness in the '2 or more attacks a week' subpopulation

Lanadelumab dose switching

3.9 The committee noted that the starting dose for lanadelumab is 300 mg every 2 weeks. This can be reduced to every 4 weeks in people whose condition is stable and attack free, especially people with low body weight. In NICE's technology appraisal guidance on lanadelumab for preventing recurrent attacks of hereditary angioedema (from here, TA606), it was assumed that 77% of people taking lanadelumab switched to every 4 weeks dosing after 1 year. The company's and EAG's preferred model assumed that 45% of people having lanadelumab switched to every 4 weeks dosing based on Dorr et al. (2023). Both models also assumed that the duration of switching was 6 months. The company's model assumed that dose switching from every 2 weeks to every 4 weeks occurred linearly across cycles over a 12-month period. The EAG disagreed that switching to every 4 weeks dosing would be gradual and instead preferred to assume it occurred instantaneously at 12 months. This was based on a real-world study in Germany by Magerl et al. (2024). To estimate the effectiveness of lanadelumab every 4 weeks, the company used the 3-arm HELP-03 trial. This included an arm in which people started lanadelumab at a dosage of 300 mg every 4 weeks. The EAG noted that people in this arm started on 4-weekly dosing (that is, they did not switch from lanadelumab every 2 weeks). The EAG preferred to assume equal efficacy of lanadelumab every 4 weeks and lanadelumab every 2 weeks. It advised that this seemed to be a reasonable assumption. This was because dose switching would occur in people whose condition was stable and attack free, and this stability and attack freedom would likely continue with less frequent dosing. The EAG added that, in its approach, if a response is not maintained in people switching to lanadelumab every 4 weeks, they switch back to having lanadelumab every 2 weeks.

The committee noted comments from stakeholders that, in UK clinical practice, transition from lanadelumab every 2 weeks to every 4 weeks would be gradual. It also acknowledged the differences in opinions expressed by the clinical experts at the second committee meeting about how the timing of dose switching should be modelled. The EAG explained that it had tested the timing of lanadelumab

dose switching (gradual or instantaneous) in sensitivity analysis. It found that it had minimal impact on the cost-effectiveness estimates. The committee noted that the company's approach likely underestimated lanadelumab efficacy. This was because it assumed the level of response is lower for lanadelumab every 4 weeks than lanadelumab every 2 weeks. So, assuming switching was gradual, and started earlier, benefitted the garadacimab arm in the model. The committee concluded that it preferred the EAG's assumptions for lanadelumab dose switching.

Treatment effectiveness in the '2 or more attacks a month' subpopulation

Berotralstat's longer-term effectiveness and stopping rule

3.10 In UK clinical practice, a stopping rule is applied for berotralstat. This means it is stopped if the number of hereditary angioedema attacks is not reduced by at least 50% after 3 months from starting treatment. The clinical experts advised that there may not be another preventive treatment that can be offered after stopping berotralstat. The committee noted that the company agreed with the EAG at the second meeting to use NMA data (see section 3.6) anchored to garadacimab for berotralstat efficacy up to month 3. The committee also noted that the berotralstat stopping rule was not implemented in the APeX trials. Also, data from TA738 on the impact of the stopping rule on berotralstat's effectiveness was considered confidential by the company that makes berotralstat. So, the company needed to make assumptions about what the efficacy (average attack rate) would be in people continuing berotralstat after 3 months (such as people whose hereditary angioedema responded to berotralstat treatment).

In its original submission, the company extrapolated the NMA results, which include the APeX trials, for the average attack rate up to month 3 to people still on berotralstat after month 3. The EAG explained that this approach used data on what would be response and non-response to berotralstat in clinical practice, so berotralstat efficacy was likely underestimated in the longer term. The EAG originally preferred a different approach. This was to assume that, after month 3,

berotralstat had the same efficacy as lanadelumab dosed every 2 weeks. The EAG explained that its preferred approach was based on clinical expert advice that hereditary angioedema that has responded to berotralstat can continue to respond very well. At technical engagement, the company disagreed with the EAG's preferred approach of using lanadelumab efficacy as a proxy for berotralstat. It argued that this was not justified given the higher likelihood of attack freedom seen in lanadelumab studies compared with berotralstat studies. Clinical experts and stakeholders commenting on the draft guidance noted that it was difficult to compare lanadelumab and berotralstat efficacy. This was because they could be used in different populations characterised by different frequency of attacks. The clinical experts at the second meeting said that, in some people, berotralstat works as well as lanadelumab. But they proposed that the 2 treatments should not be viewed as equivalent. The committee decided that the lack of clinical evidence on berotralstat taking account of the stopping rule applied in NHS clinical practice introduced high uncertainty into the modelling of berotralstat's longer-term effectiveness.

Real-world evidence for modelling berotralstat's longer-term effectiveness

3.11 At technical engagement, the company updated its approach to modelling berotralstat's effectiveness after month 3 (see section 3.10). This used real-world evidence on clinical effectiveness and patient-reported outcomes from a clinical audit of long-term preventive use (up to 24 months) of berotralstat (Elbashir et al. 2024; poster presentation). The company noted that the study included 18 UK immunology centres and more people (n=164) than the pivotal phase 3 trial of berotralstat. The company used this evidence to estimate the proportion of study participants whose hereditary angioedema responded to berotralstat and could continue treatment. It then used the average attack rate in these participants between month 12 and 24 and applied it after month 3 to people continuing berotralstat in the model. It said that the Elbashir et al. study was the best available source on efficacy in people whose condition responded to berotralstat. This was because it had a large sample size and was specific to NHS clinical practice. The EAG explained that, on balance, it thought that too little information was available on the Elbashir et al. study methods. It also thought that the limitations with the small amount of data available were too great to use it in its

base case. The EAG noted that the company's approach disregarded the NMA results for berotralstat after month 3, so it was a naive comparison.

At the second committee meeting, the company had got anonymised individual patient-level data from the Elbashir et al. study and presented a reanalysis of this. The committee thanked the study investigators for making this data available. The EAG agreed that this new analysis provided valuable data for a relevant cohort of people having berotralstat; that is, people who had 2 or more attacks a month at baseline, started treatment after the stopping rule was introduced and had a reduction in attack rate of 50% or more at month 3. So, the new analysis only included people whose condition had responded to berotralstat by month 3. But the EAG explained that the new analysis gave results that were slightly worse for berotralstat than the NMA results, which included the APeX trials used in the company's original approach (see section 3.10). The EAG advised that the results of the new analysis using individual patient-level data from Elbashir et al. lacked face validity. This is because the aim in the relevant cohort was to only continue treatment in the people whose condition best responded. So, the effectiveness of berotralstat in this cohort is expected to be better than that in the APeX trials. The stopping rule was not implemented in the APeX trials, so people whose condition had a lower response were included in the trial's efficacy estimate.

At the second meeting, the company said it preferred to take a holistic view of the efficacy of berotralstat using the real-world evidence. It suggested that the response criteria used in the analysis of individual patient-level data may have been overly strict. The EAG advised that the implausible conclusion of the Elbashir et al. results was primarily because it used data from a real-world study, but all the other effectiveness data used in the model came from clinical trials. The EAG also noted that the baseline attack rate in the Elbashir et al. cohort was much higher than that in the VANGUARD and APeX trials. So, the EAG preferred to use the intention-to-treat analysis from the NMA, which included the APeX trials (that is, the company's original approach; see section 3.10), to represent a realistic lower estimate of berotralstat effectiveness after month 3. It also noted that its earlier assumption (that after month 3 berotralstat had the same efficacy as lanadelumab dosed every 2 weeks) represented the upper estimate of berotralstat after month 3. The EAG thought that the true effectiveness of berotralstat would lie between these 2 estimates.

Taking into account new evidence from the company, EAG and clinical experts at the meeting, the committee decided that it was not appropriate to use the real-world evidence from Elbashir et al. to model berotralstat effectiveness. This was because of limitations with the evidence, and a lack of face validity in the individual patient-level results used in the company's updated base case. The committee also preferred not to assume that berotralstat had the same efficacy as lanadelumab after month 3 (which was the EAG's updated base-case upper estimate). The committee decided that the NMA data from the APeX trials (the EAG's updated base-case lower estimate and the original company base case) should be used to model the longer-term effectiveness of berotralstat. This was despite the limitations of it not including the berotralstat stopping rule. This was because it was evidence from clinical trials and was being compared with garadacimab evidence that was also from a trial and gave efficacy estimates between the other 2 approaches (company's updated and EAG's upper estimate). It also concluded that this approach was uncertain.

Utility values

Patient utilities for having an attack

3.12 The company used Nordenfelt et al. (2014), a Swedish registry study, to estimate the impact of hereditary angioedema attacks on health-related quality of life. The committee noted that this was the same source as used in TA738 (berotralstat) and TA606 (lanadelumab). This provided utility values for an attack based on EQ-5D-5L data. The utility value in the attack health state was derived from the baseline utility value (calculated by an equation in Nordenfelt et al.) minus the hereditary angioedema attack disutility based on the severity of each attack (and other technology-specific disutilities). After technical engagement, the company assumed that the impact of an attack on health-related quality of life lasted 3.13 days (Lumry et al. 2010). This duration of impact was longer than the duration of having an attack in VANGUARD. The company suggested that the impact of an attack should capture both physical and psychological acute effects. The committee recalled that the patient and clinical experts explained that it can take up to a week to recover from the effects of an attack (see section 3.1). The EAG accepted the company's baseline utility values and decrements applied for

having an attack. But the EAG preferred to assume the duration of health-related quality-of-life impact for an attack was the same as the duration of an attack in VANGUARD. The attack duration from VANGUARD cannot be reported here because the company considers it to be confidential. The committee decided that it preferred the company's assumption that the impact lasted on average 3.13 days. It noted that the company and the EAG were aligned with this committee preference at the second committee meeting. The committee concluded that it agreed with the company's and EAG's updated approach to modelling patient utilities for having an attack.

Patient utilities for being attack free

3.13 The patient and clinical experts advised that long periods of time being attack free would lead to large improvements in health-related quality of life. The clinical experts explained that, even after being attack free for 6 months, a breakthrough attack (see section 3.1) would lead to a large reduction in health-related quality of life. It would also cause a loss of all attack-free utility. They added that improvement in attack severity is also important, although this was not included in the model. The committee was concerned at the first meeting that there may have been some double counting of health-related quality of life in the company's original model. This was because the impact of an attack was modelled to last longer than the attack duration (see section 3.12). It was also because the company attempted to account for freedom from attacks in 2 ways:

- using tunnel states in the model (original approach)
- using the regression analysis in Nordenfelt et al. (2014).

The EAG preferred to assume that the benefit from attack freedom would be incurred within the first month after an attack through the application of the Nordenfelt et al. equation (without tunnel states). It noted that both the company's and EAG's clinical experts disagreed with the company's original assumption that quality of life would return to that of the general population after 6 months of being attack free. This was because of lingering fear or anticipatory anxiety about the next attack. The patient and clinical experts in the meeting noted that anticipatory anxiety and mental health effects were important considerations for the health-related quality of life of people with

hereditary angioedema. The EAG explained that, in its preferred approach, utility was only a function of time spent attack free based on the number of attacks in the previous year. People with 6 to 12 months of attack freedom in the EAG model accrued a utility value close to the general population. The committee recalled that, at the second meeting, the company removed tunnel states from its model to align with the EAG's and committee's preference at the first meeting (see section 3.7).

The EAG explained that there was ambiguity in Nordenfelt et al. about the way a decrement for attacks was calculated to take account of freedom from attacks. This was whether the decrement for 'attacks in past cycle' meant attacks in the previous 28 days or the previous year. The EAG report stated that attacks in the previous year was perhaps the more logical interpretation of the wording in the paper. So, it assumed this in its original base case. It noted that the company had assumed it was attacks in the previous 28 days. So, the EAG had initially disagreed with the company about how attack disutility was calculated. But the EAG clarified after the first meeting that its updated base case presented to committee assumed attacks in the previous 28 days, as the company had done. The EAG explained that, when it tested both scenarios, assuming attacks in the previous year gave negative utility values, which it did not consider credible. The committee noted at the second meeting that the company aligned with the EAG to assume the decrement for 'attacks in past cycle' meant in the previous 28 days. The committee decided that it preferred the EAG's simpler modelling approach that linked quality of life to time spent attack free based on the number of previous attacks. It was satisfied that this captured a health-related quality-of-life benefit for having freedom from attacks. It noted that the company's updated approach aligned with the EAG. It concluded that it agreed with the EAG's and company's updated approach to modelling utility for being attack free. It also concluded that this was associated with some uncertainty.

Carer utilities

3.14 The committee understood that hereditary angioedema could affect more than 1 person in a family, such as a parent and their child. It noted that the caring role could swap between family members depending on who was having an attack.

The company included a disutility for carers of people with recurrent attacks of hereditary angioedema in the model. The company and EAG assumed there was 1 carer for each household. The company originally estimated carer disutility for each attack using carer utilities reported by Lo et al. (2022). These were based on vignettes specifically designed to describe the hereditary angioedema context. The EAG noted that this did not align with the NICE reference case.

The company provided a statement from 8 UK healthcare professionals with experience in treating hereditary angioedema. The healthcare professionals noted that managing hereditary angioedema and having care are connected within families and can influence the occurrence of attacks. They thought that, to best characterise and elicit the impact on quality of life of carers and people with the condition, it was most appropriate to use evidence directly elicited from people living with hereditary angioedema or their carers. The EAG was uncertain whether the company's preferred vignettes might be too sensitive to hereditary angioedema, potentially leading to an overestimation of the disutility associated with the condition. The EAG noted that the size of the carer utility decrement (0.145) was large compared with decrements used in previous submissions for hereditary angioedema. The company noted that the utility decrement was adjusted for attack duration. This meant that the actual value applied was around 9-fold smaller and in line with other technology appraisals guidance on hereditary angioedema.

The EAG identified a study by Pennington et al. (2024) that used the SF-6D to measure utilities from the UK Household Longitudinal Study. It estimated carer disutility to be 0.0123 for every 0.1 patient disutility in its base case. The EAG explained that whether to include carer utility values and their size has a very limited impact on cost effectiveness. It said this was explored extensively in sensitivity analysis. The committee decided that it was reasonable for carer disutility to be included in the model. But it thought that it was likely to be overestimated using the company's original approach. At the second committee meeting, the company aligned with the EAG source for estimating carer disutility. The committee concluded that it agreed with the EAG's and company's updated approach for including carer utilities in the model, including assuming 1 carer for each household.

Severity

3.15 NICE's methods for conditions with a high degree of severity did not apply to this evaluation.

Cost-effectiveness estimates

Committees preferred assumptions

3.16 The committee concluded that the cost-effectiveness modelling for garadacimab compared with standard-care preventive treatments was uncertain (see section 3.17). It agreed with the company's model structure for decision making without tunnel states (see section 3.7). It also noted that the company aligned with the EAG's and committee's preferred assumptions at the second committee meeting for:

- the baseline attack frequency, which was based on real-world evidence (see section 3.8)
- the modelling of berotralstat efficacy up to month 3 (see section 3.10)
- the modelling of patient and carer utility values (see sections 3.12 to 3.14).

The committee's remaining preferred assumptions were:

- the EAG's modelling of lanadelumab dose switching (see section 3.9), which had a small impact on cost effectiveness for the subpopulation having 2 or more attacks a week when compared with the company's updated approach
- the EAG's modelling of berotralstat efficacy from month 3 using the NMA including APeX trial data (see section 3.10 and section 3.11).

Acceptable incremental cost-effectiveness ratio

3.17 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained,

judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- there was no evidence from trials directly comparing garadacimab with berotralstat, C1-INHs or lanadelumab (see section 3.6)
- in the assumptions that needed to be made about lanadelumab dose switching (see section 3.9)
- in the assumptions that needed to be made about berotralstat's longer-term effectiveness and stopping treatment (see section 3.10 and section 3.11)
- in patient utilities (see section 3.13).

The committee also recognised:

- the difficulties in evidence generation for hereditary angioedema because it is a rare disease
- that new evidence was obtained on real-world use of berotralstat in UK clinical practice (see section 3.11)
- the unmet need, particularly for people with an attack frequency below the eligibility criteria for lanadelumab.

The committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Cost-effectiveness estimates

3.18 Because of confidential commercial arrangements for garadacimab, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. Taking account of all

these confidential discounts, the results showed:

- Garadacimab was more effective and less costly (that is, dominated) compared with C1-INHs or lanadelumab in people having 2 or more attacks a week, in the company's and EAG's base cases and applying the committee's preferred assumptions.
- For the comparison with berotralstat for people having less frequent attacks (that is, 2 or more attacks a month) both the company's and EAG's deterministic base-case ICERs for garadacimab presented at the second meeting were substantially higher than £30,000 per QALY gained. When the committee's preferred assumptions (see section 3.16) and a revised confidential discounted price for garadacimab were applied, the plausible ICER for garadacimab compared with berotralstat was around the middle of the range NICE considers a cost-effective use of NHS resources.

  The committee concluded that garadacimab can be used as an option to prevent recurrent attacks of hereditary angioedema in people 12 years and over having 2 or more attacks a month, which includes people having more frequent attacks (that is, 2 or more attacks a week).

Other factors

Equality

3.19 The committee was aware that young people have less access to long-term preventive treatments for recurrent hereditary angioedema than adults in NHS clinical practice. It noted 2 reasons for this from the access criteria (see section 3.2):

- Age: berotralstat is only available to people 12 years and over.
- Attack frequency (2 or more attacks a month [berotralstat] or 2 or more attacks a week [C1-INHs and lanadelumab]): young people tend to have a lower attack frequency than adults, and this may be below access criteria, but they are significantly affected by the condition.

The committee noted that age is a protected characteristic under the Equality Act 2010. The marketing authorisation for garadacimab is in people 12 years and over, and any recommendation by NICE must be within the marketing authorisation. The company also positioned garadacimab in people having 2 or more attacks a month. The committee understood this positioning was consistent with NHSE's algorithm of commissioned treatment options for long-term prevention of hereditary angioedema attacks. The committee also noted that some religious groups may be unwilling to have blood-derived products, such as C1-INHs. It noted that religion is a protected characteristic under the Equality Act 2010. It also noted that both garadacimab and lanadelumab are alternatives to C1-INHs that are not derived from human plasma. The committee agreed that any recommendation would apply equally to all people regardless of protected characteristics.

Proposed uncaptured aspects

3.20 In response to the draft guidance, stakeholders suggested there were aspects of hereditary angioedema or benefits of garadacimab that were not captured in the modelling. These proposed aspects were:

- An unmet need for alternative treatment options in specific age groups:
  - people aged 1 to 16 years, who stakeholders suggested may have more side effects with berotralstat than older patients
  - people aged 12 to 25 years (in particular, people with attacks triggered by fluctuation of oestrogen), who can more easily manage attacks with an easy to administer preventive treatment at home.

    The committee recognised the unmet need for new treatment options and understood this might affect some people more than others. It heard from clinical experts at the second meeting that their experience with berotralstat was that it had more side effects, particularly abdominal effects, in adults than in younger people. The committee recalled that any recommendation would apply equally to all people regardless of protected characteristics (see section 3.19). It also decided that it had

taken account of unmet need in deciding that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (see section 3.17).

- Quality of life impacts related to attack severity and anticipatory anxiety and stress related to future hereditary angioedema attacks. The committee recognised that attack severity is distinct from attack frequency, and that its preferred assumptions did not capture treatment differences for attack severity. It noted that the disutility applied for having an attack differed by attack severity (mild, moderate, severe non-laryngeal or severe laryngeal). It also noted that the duration of an attack forms part of its severity and impact on quality of life. It noted that, in the model, the impact on quality of life of people with the condition was assumed to last longer than the average duration of an attack in the VANGUARD trial (see section 3.12). The committee decided that it preferred a simple modelling approach based mainly on attack frequency. This was because it meant that fewer assumptions were needed, which reduced uncertainty, particularly because the condition is highly variable between people. The committee decided that it took account of anticipatory anxiety related to potential future attacks by modelling the health-related quality-of-life impacts of both having attacks and being free from attacks.

- The convenience of having an effective treatment that can be self-injected at home. This included that the garadacimab autoinjector could be stored at room temperature for up to 2 months. Stakeholders suggested that this could lift key restrictions on people with the condition in terms of travelling to work and school, to visit family and for leisure purposes.

  The committee decided that the effectiveness of garadacimab was already captured in the model. It also decided that convenience and portability of garadacimab was relative to C1-INHs or lanadelumab, in particular because berotralstat was an oral treatment. But it acknowledged that not everyone can take oral treatments (see section 3.2). The committee concluded that it had recognised unmet need in deciding on an acceptable ICER for decision making. It also concluded that no adjustments were needed to take account of the proposed uncaptured aspects in its preferred ICER or in its conclusions on the cost effectiveness of garadacimab.

Conclusion

Recommendation

3.21 The committee acknowledged there is an unmet need for long-term preventive treatments for recurrent attacks of hereditary angioedema. It noted that this included people having fewer than 2 attacks a week who are not eligible to have C1-INHs or lanadelumab. It concluded that for people having 2 or more attacks a week, garadacimab dominated the comparators so was a cost-effective option. It also concluded that for people having 2 or more attacks a month, the most plausible ICER was around the middle of the range normally considered a cost-effective use of NHS resources. So, the committee recommended garadacimab as an option for preventing recurrent attacks of hereditary angioedema in people 12 years and over, only if they have 2 or more attacks a month (which includes people having more frequent attacks; that is, 2 or more attacks a week).

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has recurrent hereditary angioedema and the healthcare professional responsible for their care thinks that garadacimab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas
Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical, a project manager and an associate director.

Catherine Spanswick
Technical lead

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Project managers

Ross Dent
Associate director

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