NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Sebetralstat for treating hereditary angioedema attacks in people 12 years and over

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using sebetralstat in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: October 2025

Note that this document is not NICE's final guidance on sebetralstat. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using sebetralstat in the NHS in England.

For further details, see NICE's manual on health technology evaluations.

The key dates for this evaluation are:

- Closing date for comments: 25 November 2025
- Second evaluation committee meeting: 09 December 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Sebetralstat should not be used to treat hereditary angioedema attacks in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with sebetralstat 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

Sebetralstat is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether sebetralstat is value for money in this population.

Why the committee made these recommendations

Usual treatment of acute hereditary angioedema attacks in people 12 years and over includes icatibant or a C1-esterase inhibitor (C1-INH) such as Berinert, Cinryze or Ruconest.

Clinical trial evidence shows that symptom relief starts sooner and attacks end faster with sebetralstat than with placebo. An indirect comparison suggests that sebetralstat may work as well as Ruconest. But these results are uncertain. This is because there are differences between the sebetralstat and Ruconest trials, and the indirect comparison only looked at time to the start of symptom relief. There is no

evidence on how well sebetralstat works compared with Berinert, Cinryze or icatibant.

There are uncertainties with the economic model, including:

- a lack of evidence on how long it takes for an attack to end with sebetralstat compared with usual treatment
- the analyses used to estimate treatment effects for sebetralstat and usual treatment.

Because of the uncertainties in the clinical evidence and economic model, it is not possible to determine the most likely cost-effectiveness estimates for sebetralstat. So, sebetralstat should not be used.

2 Information about sebetralstat

Marketing authorisation indication

2.1 Sebetralstat (Ekterly, KalVista) is indicated for 'the treatment of hereditary angioedema (HAE) attacks in adult and adolescents aged 12 years and older'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of sebetralstat is £12,000 for a 300-mg pack of 6 tablets (including VAT, company submission).

2.4 The company has a commercial arrangement, which would have applied if sebetralstat had been recommended.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for KalVista will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by KalVista, 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.

The condition

3.1 Hereditary angioedema is a rare genetic disorder. It is almost always caused by a mutation in the gene for C1-esterase inhibitor (C1-INH), known as type 1 or type 2 hereditary angioedema. A third, much rarer, subtype is caused by other mutations, known as hereditary angioedema with normal C1-INH. Hereditary angioedema is a chronic, relapsing condition involving recurrent unpredictable attacks of swelling in areas of the skin and deeper tissues. Symptoms vary depending on where in the body the attack happens (attack location). Swelling of the airway can be life threatening, but the condition does not affect life expectancy when there is appropriate treatment and management. Attacks can cause severe pain and affect the ability to carry out usual activities. The patient submissions highlighted that attacks happen very quickly and typically last a few days, followed by a recovery period. The patient and clinical experts explained that all people with hereditary angioedema experience attacks differently. They highlighted that the severity and frequency of previous attacks does not predict how future attacks will present. The patient experts described how the uncertainty around when an attack may occur causes anxiety for people with hereditary angioedema and that this anxiety itself can trigger an attack. They also explained that attacks can substantially affect the quality of life for people with this condition, as well as that of their family members and carers. The committee recognised that acute attacks of hereditary angioedema can be serious, debilitating and substantially impact quality of life.

Treatment pathway

Current treatment and unmet need

3.2 On-demand treatments for attacks in people with type 1 or type 2 hereditary angioedema are based on NHS England's algorithm of commissioned treatment options for hereditary and acquired angioedema secondary to C1-INH deficiency (PDF only). This includes icatibant (given by subcutaneous injection) or C1-INHs (Berinert, Cinryze or Ruconest [also called conestat alfa], given by intravenous injection), referred to as standard care. For adults with hereditary angioedema with normal C1-INH, NHS England's clinical commissioning policy on icatibant for treating moderate to severe acute swellings due to bradykinin-mediated angioedema with normal C1 inhibitor (PDF only) applies. Treatments may be self-administered or given in a hospital (for example, an emergency department) that has access to on-demand treatments. The committee understood that on-demand treatments treat individual attacks but may not prevent future attacks or make them less severe. The patient and clinical experts explained that on-demand treatments can be painful to administer, cause anxiety (particularly for people with a fear of needles), and are difficult to carry around because they need refrigeration. The clinical submissions and patient experts highlighted that these challenges can delay treatment, leading to attack progression and poorer outcomes. The patient experts explained that some people find it difficult to self-administer treatment and often need help from a carer. The committee noted that sebetralstat offers benefits over current treatments because of its oral formulation. This makes it more convenient to transport and less invasive to self-administer. It concluded that people with hereditary angioedema would welcome another treatment option.

Positioning of sebetralstat and comparators

3.3 The company positioned sebetralstat as an alternative to icatibant and C1-INHs for the first-line treatment of hereditary angioedema attacks in people 12 years and over. The clinical experts confirmed that icatibant

and C1-INHs were the most relevant comparators for sebetralstat. They explained that icatibant is often considered first because it is easier to self-administer and cheaper than C1-INHs. They further explained that treatment choice is also largely guided by individual preference and efficacy. For example, some people may prefer a C1-INH because icatibant may not manage their attacks as effectively and it can be more painful to administer. The clinical experts explained that a small proportion of people may have access to both types of on-demand treatment. This is so they can choose the most appropriate treatment based on their circumstances at the time of the attack, including attack location or need for rescue therapy (if there is a lack of response to the first treatment). The committee concluded that the company's positioning of sebetralstat and its comparators was appropriate.

Subtypes in decision problem

3.4 The population in the final scope included 'people 12 years and over with hereditary angioedema having an acute attack'. The committee noted that the company submission only included type 1 and type 2 hereditary angioedema, which was narrower than the population in the scope and the marketing authorisation for sebetralstat. The company said this was because the third subtype, hereditary angioedema with normal C1-INH, is very rare and that it did not have any data to support sebetralstat use in this population. The clinical experts said that treatment options for the third subtype are very limited (see NHS England's clinical commissioning policy on icatibant for treating moderate to severe acute swellings due to bradykinin-mediated angioedema with normal C1 inhibitor [PDF only]). They explained that while this subtype is caused by various mutations, they would still expect sebetralstat to be as effective as icatibant for some people in this group. The committee recognised the unmet need for treatments for hereditary angioedema with normal C1-INH but thought that the effectiveness of sebetralstat in this population was unknown. It concluded that, based on the evidence presented, it could only consider sebetralstat for type 1 and type 2 hereditary angioedema. It further

concluded that evidence supporting the efficacy of sebetralstat for the third subtype, or, if not available, evidence of biological plausibility to justify generalising clinical efficacy data to the third subtype, may help to reduce this uncertainty.

Clinical evidence

Data sources

3.5 The key clinical evidence for sebetralstat came from the KONFIDENT trial. This was a phase 3, double-blind, randomised, 3-way crossover trial. The population included people 12 years and over with type 1 or type 2 hereditary angioedema. People in the trial (n=136) were randomised to 1 of 6 treatment sequences to take sebetralstat (300 mg or 600 mg) or placebo for 3 eligible attacks. Randomisation was stratified on the use of long-term preventive treatment at the time of enrolment. An optional second dose (matching the first dose) could be taken if needed at least 3 hours after the first dose. The EAG thought that the washout period (48 hours) was sufficient to reduce any crossover with previous treatment, because the half-life of sebetralstat is around 3 hours. It thought that KONFIDENT was at low risk of bias. The committee noted that there was no trial data that directly compared sebetralstat with icatibant or C1-INHs. It also noted the recommended dose in the summary of product characteristics for sebetralstat is 300 mg. It concluded that KONFIDENT was appropriate for decision making but that it did not directly compare sebetralstat with standard care. It noted the KONFIDENT-S open-label extension study assessing the long-term safety and efficacy of sebetralstat was ongoing.

Clinical effectiveness

3.6 The primary outcome in KONFIDENT was the time to beginning of symptom relief. Symptom relief was defined as a rating of at least ‘a little better’ on the Patient Global Impression of Change (PGI-C) scale for 2 or more consecutive time points within 12 hours of administration of

sebetralstat or placebo. The PGI-C is a 7-point scale with ratings ranging from 'much better' to 'much worse'. In the full analysis set, the time to beginning of symptom relief was significantly shorter with sebetralstat (adjusted p<0.001 for the 300-mg dose compared with placebo). The median time to beginning of symptom relief was 1.61 hours for the 300-mg dose compared with 6.72 hours for placebo. Key secondary outcomes included the time to reduction in attack severity within 12 hours of administration and time to attack resolution (TTAR) within 24 hours of administration. In the full analysis set, sebetralstat significantly improved both outcomes compared with placebo. The company presented results from both 300-mg and 600-mg doses from the trial. It assumed equivalence between the 300-mg and 600-mg doses of sebetralstat because the hazard ratios showed no statistical difference for primary and key secondary outcomes. The EAG thought that this assumption was reasonable. The committee concluded that sebetralstat is an effective treatment for acute hereditary angioedema attacks.

Indirect treatment comparison

3.7 The company presented results from an indirect treatment comparison (ITC) of sebetralstat with a C1-INH (Ruconest). This included a network meta-analysis for the outcome of time to beginning of symptom relief. It included KONFIDENT (sebetralstat 300 mg compared with placebo) and a published phase 3 trial (Ruconest 50 IU/kg compared with placebo, Riedl et al. 2014). The results suggested no significant difference between treatments using fixed or random effects models. Matching-adjusted indirect comparisons (MAICs) were also done for the outcome of time to beginning of symptom relief. The population from KONFIDENT (total attacks, n=171) was matched to the population from Riedl et al. (n=75). The MAICs were either matched for attack severity (scenario 1) or for attack severity plus age, sex and race (scenario 2). The results from the MAICs suggested that there was no significant difference in the time to beginning of symptom relief between treatments in either scenario. The EAG thought that several important prognostic variables (subtype of

hereditary angioedema, comorbidity and baseline attack frequency) had not been adjusted for in the MAIC analyses because of a lack of data. It believed that this may have compromised the validity of results. The clinical and patient experts explained that prognostic variables are less useful for hereditary angioedema because each attack is different and unpredictable in both timing and severity. The clinical experts explained that long-term preventive treatments were unlikely to alter the severity of an attack. The company said that this was supported by data from KONFIDENT. The company explained that it is difficult to do reliable ITCs for on-demand treatments for hereditary angioedema because of the heterogeneity in trial designs and definitions of endpoints. The committee concluded that the results from the ITC were uncertain and did not compare sebetralstat with Berinert, Cinryze or icatibant.

Assumption of clinical equivalence

3.8 No direct evidence was available for sebetralstat compared with icatibant or C1-INHs, and results from an ITC were uncertain and did not include a comparison with Berinert, Cinryze or icatibant (see section 3.7). The clinical experts thought that on-demand treatments were broadly comparable in how effectively they resolve symptoms once administered, based on their clinical experience. They explained that in the KONFIDENT-S open-label extension study, people switched from icatibant to sebetralstat without experiencing any reduction in effectiveness for treating attacks. The clinical experts highlighted that because icatibant has a shorter half-life, this often results in a higher rate of additional dosing compared with C1-INHs. The patient experts said that treatment response to icatibant varies, but that C1-INHs are generally very effective for most people. The clinical experts explained that the severity or duration of attack is not affected by the method of administration but can be affected by the time taken to administer treatment. This is because earlier use of treatment stops the swelling from becoming established and this shortens the attack duration. They explained that on-demand treatments do not reduce any existing swelling

but can prevent further attack progression. The committee noted that it is plausible that oral sebetralstat, subcutaneous icatibant and intravenous C1-INHs have different rates of absorption and onset of action, given they have different routes of administration. But it noted that the company did not provide data that supports that these were equal between treatments. The committee concluded that it would like to see further evidence to support the assumption of clinical equivalence for time to symptom resolution across all standard care treatments. It also requested additional evidence to support equal rates of absorption and onset of action for sebetralstat and its comparators, or if this unavailable, the biological rationale for comparable rates of action.

Time to attack resolution

3.9 The key efficacy outcome in the economic model was TTAR, which was estimated based on the time to treatment administration (TTA) after an attack (see section 3.11). This was because the company assumed that earlier administration of on-demand treatment results in a shorter total attack duration. The committee noted that the company was unable to do an ITC for the TTAR outcome. Because of this, it thought that the MAICs (see section 3.7) had limited relevance for assessing clinical equivalence in TTAR between sebetralstat and its comparators, particularly for icatibant. It agreed that it would have liked to have seen clinical evidence comparing TTAR between treatments. The committee recognised that TTA is likely influenced by the method of administration for each on-demand treatment. But that it was unclear whether this was because earlier administration of treatment would likely reduce the severity of attack and that this would shorten its duration. The committee concluded that it would like see evidence that shows that the reduction in attack severity does not influence TTAR for sebetralstat and its comparators.

Economic model

Company's modelling approach

3.10 The company presented a cohort state transition model with 2 health states in its base case: alive, and dead because of natural mortality. The model cohort was split into long-term prophylaxis with on-demand treatment (45%) or on-demand treatment only (55%). This was used to calculate an average attack rate of 14.7 attacks per year. Attacks were modelled as acute transient events within the alive health state with a constant cycle-level risk over time. Use of additional doses (same on-demand treatment) and rescue therapy (alternative on-demand treatment) were fixed per cycle and treatment-specific. Mortality rates were applied from UK general population life tables and adjusted by cycle, age and gender. The company explained that this was because mortality from hereditary angioedema is very rare and usually occurs in people not yet diagnosed. The model included 3 attack locations (neck and above, abdomen, and other) to estimate the impact of acute attacks on health-related quality of life. The model included a 21-day cycle and applied a half-cycle correction over a lifetime time horizon.

The EAG noted that the model produced counterintuitive results for some scenarios in which certain inputs were varied to increase disease burden. The company explained that this could be resolved by switching off the between-attack disutilities in the model. This is because disutilities between attacks were only applied when attacks were not occurring, to avoid double counting. The committee remained uncertain as to whether the company's explanation would fully resolve the counterintuitive results identified by the EAG. It thought that it was unclear why the company had modelled a lifetime time horizon instead of a single acute attack. The company explained that modelling a single acute attack may not capture the full burden of hereditary angioedema. The patient experts explained that an oral treatment would likely reduce anticipatory anxiety between attacks because it is more portable and avoids the need for injections.

The committee noted that the company had not provided any evidence to support this assumption. It recalled that use of on-demand treatments and the speed of administration for a single attack may not affect the severity or frequency of future attacks, although it asked to see further evidence on this. It concluded that it would like to see model-based analyses that also consider the impact of a single attack instead of a lifetime time horizon. It noted that this approach would also align with how other on-demand treatments have been modelled for hereditary angioedema and for other acute conditions in previous NICE evaluations.

Lack of comparative clinical data

3.11 In the absence of any comparative evidence for TTAR between sebetralstat and its comparators, the company's model applied a hazard ratio to adjust TTAR based on TTA. This meant that TTA was the only driver of differential efficacy in the model. The hazard ratio was estimated using a Cox proportional hazards regression analysis. This included variables for treatment sequence, attack number, baseline attack severity, baseline attack location and TTA. The analysis used mean TTA data for sebetralstat from the KONFIDENT-S open-label extension study (the company considers the figure to be confidential so it cannot be reported here). The mean TTA for icatibant was around 2.9 hours (from Longhurst et al. 2018) and the mean TTA for C1-INHs was around 3.8 hours (from Christiansen et al. 2024). The committee queried whether the TTA for icatibant may now be shorter in clinical practice because the data source was from 2018. The patient experts described how people often delay treatment with icatibant, because they struggle to self-administer the injection, particularly if the attack causes swelling of the hands. The clinical experts explained that people often wait until they are certain they are having an attack before using icatibant, because the injection can be painful. They thought the icatibant TTA estimate was reasonable but noted that TTA would likely be longer for C1-INHs because they are typically administered in hospital. The committee noted that the TTA distributions were skewed for icatibant and the C1-INHs, and so using the

mean value may not be the most appropriate. The EAG said that it had explored using the upper and lower bounds of the interquartile range from the reported median value in scenario analyses. The committee agreed with the EAG's concerns about the regression analysis, including that the Cox model was retrospective, non-comparative and not pre-specified, increasing the risk of bias. It further agreed that the regression analysis should be re-estimated to only include covariates which are consistent with the model inputs, specifically TTA and attack location. The committee noted that the Cox model may overestimate TTA and therefore TTAR for all treatments, by not accounting for additional doses or rescue treatment. The company explained that its approach to estimating the relationship between TTA and TTAR for on-demand treatments was supported by published evidence. The committee noted that it had not been presented with this evidence. It concluded that the company's approach to estimating treatment effects in the model was highly uncertain. The committee recalled that the company did not provide data which showed that the rates of absorption and onset of action were equal between treatments. The committee was concerned this meant that assuming TTA is the only driver of efficacy was highly uncertain, because a shorter TTA may not correlate directly to a faster onset of action. It requested:

- further evidence to support the use of a Cox model to estimate TTAR from TTA for on-demand treatments and to explore using estimates from published data sources to inform this relationship
- a re-estimated regression analysis that only includes covariates which are consistent with the model inputs, specifically TTA and attack location
- additional evidence exploring the impact of using alternative summary statistics for TTA (other than the mean) in the regression analyses.

Definition of comparators

3.12 The company defined the comparators (icatibant and C1-INHs) as a basket of treatments because it believed that this reflected how on-

demand treatments are used in clinical practice. It referred to section 4.2.17 of NICE's manual on health technology evaluations which states 'in exceptional circumstances, if the technologies form part of a class of treatments, and evidence is available to support their clinical equivalence, estimates of quality-adjusted life years (QALYs) gained for the class as a whole can be shown'. The company explained that while on-demand treatments can differ in their mechanism of action, they are functionally substitutable and differences in efficacy are largely driven by TTA. It said that treatment choice is individualised and not determined by sequence. The clinical experts agreed that it was appropriate to consider the comparators as a class of treatments based on how they work and are used in clinical practice. The EAG believed that a class of treatments includes those with the same or similar mechanism of action, and that this was not the case for icatibant and C1-INHs. It said that the company had not presented evidence to support clinical equivalence, and substitution between treatments is uncommon in clinical practice. This is because alternative treatments would mostly be used as rescue therapy. The EAG thought that the company's basket approach was inappropriate and that sebetralstat should be considered separately with each comparator in a fully incremental analysis. The committee agreed with the EAG and concluded that a fully incremental analysis was the most appropriate approach based on the evidence presented. It noted that grouping the C1-INHs together was acceptable, because they share the same mechanism of action and administration method.

Proportions using treatments in the model

3.13 The company used market share data from a hospital pharmacy audit to estimate the use of comparators included in the basket of treatments. The EAG noted that the cost-effectiveness results were highly sensitive to changes in market share and the proportion of people needing additional dosing or rescue therapy. The committee discussed NHS England's estimate of icatibant use. It noted that this estimate aligned with that of the EAG's clinical experts but was higher than the company's modelled value

(the exact figures are confidential and cannot be reported here). The clinical experts explained that it was difficult to estimate the use of on-demand treatments but that the NHS England estimates were the most likely to reflect clinical practice. They explained that these estimates may not accurately reflect the use of Berinert or Cinryze as on-demand treatments, because they are also used for long-term prophylaxis. The committee considered the NHS England estimates to be the most appropriate for informing the proportion of people having on-demand treatment in the model. But it recalled its previous conclusion that a fully incremental analysis was more appropriate, which meant the proportions had a smaller impact on the cost-effectiveness results.

The committee noted the rate of additional dosing for sebetralstat (22.25%), sourced from the KONFIDENT-S open-label extension study, was higher than for icatibant (8.91%), Cinryze and Ruconest (18.18%), and Berinert (1.11%). NHS England advised that additional dosing for Cinryze should be equivalent to Berinert at 1.11%. The clinical experts explained that the additional dosing rate for sebetralstat would be expected to reduce over time. This was supported by evidence from the KONFIDENT-S open-label extension study which showed that people tend to use sebetralstat less frequently as they become more familiar with treatment. The committee noted the clinical expert opinion that sebetralstat additional dosing may reduce in the future. But, in the absence of supporting evidence, it concluded that the additional dosing rates for sebetralstat, icatibant and Ruconest were appropriate. It agreed that the additional dosing rate for Cinryze should align with Berinert (at 1.11%) in line with estimates from NHS England. It noted that the company's and EAG's base cases included different proportions of rescue therapy use with icatibant. The committee preferred the EAG's estimate (9.78%) because it:

- was derived from same data source as the estimate for additional dosing with icatibant (Aberer et al. 2017)

- represented a weighted average of use in people having long-term prophylaxis with on-demand treatment and those having only on-demand treatment.

  It concluded that the cost-effectiveness analyses should be updated to reflect its preferred assumptions on the proportion of people using treatments, including as additional dosing and rescue therapy.

Drug wastage

3.14 The company's base-case analysis assumed drug wastage for weight-based intravenous treatments (C1-INHs). It did this by rounding up the calculated weight-based dose to the nearest 0.2-vial increment. The committee noted that this approach assumed that partial vials can be used in 20% increments. The company explained it believed this was a conservative assumption. The EAG noted that this assumption reduced the estimated drug wastage compared with a full-vial wastage approach. But, it thought that the approach was uncertain because the company had not provided a clear justification for it. The clinical experts explained that, in clinical practice, doses would be rounded up to the nearest full vial. They explained that this approach is thought to be safe and helps to ensure adequate replacement of the C1-INH protein. The committee noted that, based on clinical expert opinion and the rarity of the condition, it may be plausible that full-vial wastage would occur for weight-based intravenous treatments in clinical practice. But it noted the extent of vial wastage was highly uncertain, particularly when taking into account subsequent dosing. It concluded that it was appropriate to assume that some vial wastage occurs for weight-based intravenous treatments. But it would like further evidence to justify the extent of vial wastage and how dose banding and additional dosing may impact this. It noted that increasing the amount of vial wastage resulted in a large decrease in the ICER.

Utility values

3.15 KONFIDENT did not collect health-related quality of life data. The company base case included a disutility for acute attacks based on the attack location. This was informed by a time trade-off analysis by Lo et al. (2022). The company applied UK general population utility values for baseline health states across all treatments modelled (adjusted over time using age- and gender-specific norms). Disutilities were included for administration method and injection-related side effects. This was informed by a discrete choice experiment commissioned by the company. The company base case did not apply a disutility difference between subcutaneous and oral administration, because the result was not statistically significant. The EAG recognised that oral administration may offer advantages over subcutaneous administration. It provided a scenario with the utility difference applied which resulted in a large reduction in the ICER. Although the EAG noted potential limitations in the modelled utilities, it thought that changes in health-related quality of life inputs were unlikely to significantly increase the ICER. The committee concluded that the company's approach to modelling utilities was appropriate, but uncertain because of the modelled time horizon and application of disutilities between attacks.

Severity

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

Cost-effectiveness estimates

Acceptable ICER

3.17 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per 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:

- a lack of evidence on the efficacy of sebetralstat in people with hereditary angioedema with normal C1-INH
- no direct evidence comparing sebetralstat with the relevant comparators
- no indirect evidence comparing sebetralstat with Cinryze, Berinert and icatibant
- no comparative data for TTAR, which is the key efficacy outcome used in the model
- the post-hoc Cox proportional hazards regression analysis that estimated TTAR based on TTA for all treatments
- the level of vial wastage that would occur for weight-based intravenous on-demand treatments.

The committee concluded that it could not determine an acceptable ICER, but because of the level of uncertainty it was at the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The committee noted it would reconsider this once further analyses have been provided.

EAG amendments to the model

3.18 The EAG made several amendments to the model to inform its base case. These included:

- using the electronic market information tool (eMIT) price for icatibant
- using life tables for mortality based on data from 2016 to 2018 (before COVID-19)
- assuming 9.78% of people using icatibant have rescue therapy (see section 3.13)
- assuming that the time needed to administer icatibant by a healthcare professional is 20 minutes, in line with clinical expert opinion

- comparing sebetralstat separately with each comparator in a fully incremental analysis.

The committee understood that the EAG had used the eMIT price for icatibant in line with NICE's process for the preferred order of prices for modelled treatments. It noted that the EAG had used the median value for the time needed to administer icatibant by a healthcare professional rather than the mean value of 1 hour used in the company base case (for both icatibant and C1-INHs). The EAG said this was because a subcutaneous treatment would likely be easier to administer and need less preparation time than an intravenous treatment. The committee understood that the estimates only reflected the duration of time needed to administer treatment whereas the modelled TTA for icatibant (around 2.9 hours) included the time between the start of an attack until treatment administration. The clinical experts explained that it was difficult to estimate the time needed to administer icatibant by a healthcare professional because most people self-administer treatment. Given this uncertainty, the committee considered the EAG's approach of using a more conservative estimate was reasonable, assuming less time for healthcare professionals to administer icatibant. The committee noted that the EAG-preferred assumptions using the eMIT price for icatibant and a fully incremental analysis had a substantial impact on the ICER. But that all the other EAG changes to the model had a small impact on the cost-effectiveness results. It concluded that the EAG amendments to the model were appropriate.

Cost-effectiveness estimates and additional evidence

3.19 The exact ICERs are confidential and cannot be reported here because they include confidential discounts for sebetralstat and C1-INHs. The company base-case ICER comparing sebetralstat with a basket of treatments was considerably higher than £30,000 per QALY gained. The EAG base-case ICER comparing sebetralstat with icatibant was considerably higher than the company base-case results (C1-INHs were

dominated in a fully incremental analysis). The committee concluded that it was unable to determine a committee-preferred base-case ICER, or determine an acceptable ICER. This is because of additional information it would like to see from the company to address uncertainties in the clinical and economic evidence. Specifically, the committee requested:

- evidence supporting the efficacy of sebetralstat for hereditary angioedema with normal C1-INH or, if not available, the biological plausibility of efficacy (see section 3.4)
- evidence supporting the clinical equivalence of icatibant with C1-INHs for time to symptom resolution (see section 3.8)
- evidence to show comparable rates of absorption and onset of action between on-demand treatments, or, if not available, the biological rationale for comparable rates of action (see section 3.8)
- evidence to show how the timing and method of treatment administration after the onset of an attack affects attack severity and TTAR (see section 3.9)
- model-based analyses which also consider the impact of a single attack instead of a lifetime time horizon (see section 3.10)
- evidence to support the use of a Cox proportional hazards model to estimate TTAR from TTA for on-demand treatments and explore using estimates from published data sources to inform this relationship (see section 3.11)
- re-estimating the Cox model to only include covariates that are consistent with the model inputs (see section 3.11)
- evidence exploring the impact of using alternative summary statistics for TTA in the regression analyses (see section 3.11)
- evidence to justify the extent of vial wastage for weight-based intravenous on-demand treatments and how dose banding and additional dosing may impact this (see section 3.14).

The committee concluded that it was unable to determine the most plausible ICER because of the uncertainty in the clinical and economic evidence.

Other factors

Equality

3.20 The committee noted that current on-demand treatments for people with type 1 or type 2 hereditary angioedema are available to people of all ages, but that sebetralstat is only licensed for people 12 years and over. It noted that it could only recommend sebetralstat within its marketing authorisation. The committee also recalled that it had not been presented with sufficient evidence on sebetralstat in people with hereditary angioedema with normal C1-INH (see section 3.4). It noted that some religious groups may be unwilling to have blood-derived products, such as C1-INHs. It recognised that religion is a protected characteristic under the Equality Act 2010. It noted that icatibant is an alternative to C1-INHs that is not derived from human plasma or animal products, so is available to this population. It also noted that icatibant is the most common treatment used by people with hereditary angioedema for acute attacks.

Uncaptured benefits

3.21 The committee recognised that because sebetralstat is the first oral on-demand treatment it may have advantages over current treatments which are given by injection. It recalled that the patient expert considered that an oral treatment may potentially reduce anxiety between attacks. The committee noted that this had not been captured in the economic model and that it had not seen any evidence to support this assumption (see section 3.10). Further evidence should be provided to show that an on-demand treatment for a single attack does not affect the severity or frequency of future attacks but can reduce anxiety between attacks (see section 3.10). It did not identify any other additional benefits of sebetralstat not captured in the economic modelling. So, the committee

concluded that all additional benefits of sebetralstat had already been taken into account.

Conclusion

3.22 The committee concluded that it had not been presented with a cost-effectiveness estimate that was suitable for decision making. So, it could not recommend sebetralstat for treating hereditary angioedema attacks in people 12 years and over.

4 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

Charles Crawley
Chair, technology appraisal committee B

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 adviser, a project manager and an associate director.

Anita Sangha

Technical lead

Nigel Gumbleton

Technical adviser

Leena Issa

Project manager

Lorna Dunning

Associate director

ISBN: [to be added at publication]