**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Health Technology Evaluation**

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

**Final scope**

## Final remit/evaluation objective

To appraise the clinical and cost effectiveness of sebetralstat within its marketing authorisation for treating acute attacks of hereditary angioedema.

## Background

Hereditary angioedema (HAE) is a rare genetic disorder, associated with a deficiency or dysfunction of the protein C1-esterase inhibitor, which regulates inflammatory pathways. Usually, C1-esterase inhibitor controls enzyme cascade reactions to prevent uncontrolled swelling of the subcutaneous and submucosal tissues. In people with HAE, particularly during times of physiological or psychological stress, the function of the C1-esterase inhibitor is insufficient, resulting in the accumulation of excessive fluid (oedema) and localised oedematous swellings. The swellings often occur in the mouth (which may cause difficulty with eating and speaking), the gut (which may affect the submucosal tissues and cause abdominal pain, nausea, or vomiting), and the airway (which may lead to breathing difficulties or potential asphyxia). The swellings can also affect the deep tissues of the skin (involving the dermis and subcutaneous tissues), with significant impact, especially when the hands, feet or genitals are involved. HAE attacks are associated with disfiguration, severe pain, an inability to perform daily activities and feelings of fear and anxiety.

Many angioedema attacks are associated with triggers such as trauma, medical procedures, emotional stress, menstruation, oral contraceptive use, infections, or the use of medications such as ACE inhibitors. But often, a specific trigger cannot be identified. Attacks are unpredictable and the severity and frequency of previous attacks do not predict future attacks. Attacks typically last 2 to 5 days before resolving spontaneously.

There are 3 types of HAE. Types I (approximately 85%) and II (approximately 15%) are a result of a known genetic mutation and account for almost all cases of HAE[1]:

- Type I is characterised by low levels of C1-esterase inhibitor in the plasma.
- Type II is characterised by normal levels of a dysfunctional C1-esterase inhibitor in the plasma.
- HAE with normal C1-esterase inhibitor (previously referred to as type III) is a group of very rare diseases and is not a result of the deficiency or dysfunction of the C1-esterase inhibitor protein.[2]

It is estimated that type I and type II HAE affect at least 1 per 59,000 of the UK population and can affect people of any ethnic group or gender.[1,3] HAE usually presents in childhood, with the mean age of onset being between 8 and 12 years. Attacks are rare before the age of 2, and tend to become more frequent after adolescence.[1]

There are 3 approaches to managing HAE: avoiding factors that trigger HAE attacks (e.g. minor trauma, hormone replacement therapy), preventive (prophylactic) treatments and acute treatments. Preventive treatments can be used short-term to prevent attacks before triggers or used long-term to reduce the frequency of acute attacks.

Treatments for acute attacks of hereditary angioedema include icatibant and C1-esterase inhibitors (C1-INH) such as Cinryze, Berinert, and Ruconest.

### The technology

Sebetralstat (brand name unknown, KalVista Pharmaceuticals) does not currently have a marketing authorisation in the UK for treating acute attacks of HAE in people 12 years and over. It has been studied in phase 3 clinical trials for on-demand treatment of HAE attacks in people 12 years and over with a clinical diagnosis of C1-inhibitor (type I or type II) HAE.

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| **Intervention(s)** | Sebetralstat |
| **Population(s)** | People 12 years and over with hereditary angioedema having an acute attack |
| **Comparators** | Established clinical management for the treatment of acute attacks of hereditary angioedema which may include:<br>• C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest)<br>• Icatibant |
| **Outcomes** | The outcome measures to be considered include:<br>• severity of angioedema attacks<br>• duration of angioedema attacks<br>• time to beginning of symptom relief<br>• reduction in symptoms of angioedema attacks<br>• mortality<br>• use of rescue medication<br>• frequency and duration of hospitalisation<br>• adverse effects of treatment<br>• health-related quality of life (for patients and carers). |

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| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br><br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br><br>Costs will be considered from an NHS and Personal Social Services perspective.<br><br>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. |
| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. |
| **Related NICE recommendations** | **Related technology appraisals:**<br><br>Berotralstat for preventing recurrent attacks of hereditary angioedema (2021) NICE technology appraisal guidance 738.<br><br>Lanadelumab for preventing recurrent attacks of hereditary angioedema (2019) NICE technology appraisal guidance 606. |
| **Related National Policy** | The NHS Long Term Plan (2019) NHS Long Term Plan<br><br>NHS England (2023) Manual for prescribed specialist services (2023/2024) chapter 59, 115 and 115A<br><br>NHS Commissioning Board (2013) Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema |

**References**

1. NHS Clinical commissioning: plasma derived C1-esterase inhibitor for prophylactic treatment of HAE (2016). Accessed May 2024 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/16045_FINAL.pdf

2. Maurer M, Magerl M, Betschel S, et al.The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update.Allergy. 2022;77:1961–1990. (2021)

3. Yong PFK, Coulter T, El-Shanawany T, et al. A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom. Journal of Allergy and Clinical Immunology: In Practice. 2023.