NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

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

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of donidalorsen within its marketing authorisation for preventing recurrent hereditary angioedema attacks.

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 (85%) and II (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 level 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 disease and is not a result of the deficiency or dysfunction of the C1-esterase inhibitor protein. However, it is known that oestrogen has a role not yet fully understood.[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 rarely occur before two years of age and are less frequent before adolescence.[1]

There are 3 approaches to managing HAE: avoidance of factors that trigger HAE (e.g. minor trauma, hormone replacement therapy), acute treatment (on-demand therapy) and preventive treatments (long-term or short-term prophylactic). Avoidance of trigger factors is not usually sufficient to control HAE attacks as they often occur randomly without any triggers. Short-term preventive treatments aim to prevent an attack before known triggers for example, dental work or surgery. Long-term preventive treatments are used routinely to reduce the need for treatment of acute attacks. As a long-term strategy attenuated androgens or C1-esterase inhibitors (C1-INH) such as Cinryze, Ruconest or Berinert can be used. Anti-fibrinolytics, such as tranexamic acid, can also be used. However, attenuated androgens and anti-fibrinolytics are not considered first-line where there are other approved medications for long-term prophylaxis treatment.[4]

NICE Technology Appraisal 606 recommends lanadelumab for preventing recurrent attacks of hereditary angioedema in people aged 12 and older, only if they are eligible for preventative C1-INH in line with NHS England's commissioning policy and the lowest dosing frequency of lanadelumab is used when the condition is in a stable, attack-free phase.

NICE Technology Appraisal 738 recommends berotralstat for preventing recurrent attacks of hereditary angioedema in people 12 years and older, only if they have at least 2 attacks per month and it is stopped if the number of attacks per month does not reduce by at least 50% after 3 months.

The technology

Donidalorsen (brand name unknown, Otsuka Pharmaceuticals) does not currently have a marketing authorisation in the UK for preventing hereditary angioedema attacks in people 12 years and over. It has been studied in phase 3 clinical trials to prevent HAE attacks in people 12 years and over with a clinical diagnosis of C1-inhibitor (type I or type II) HAE.

Intervention(s)	Donidalorsen
Population(s)	People 12 years and over with hereditary angioedema
Comparators	Established clinical management for preventing hereditary angioedema attacks, which may include: • C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest) • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat • Garadacimab (subject to NICE evaluation)

Outcomes	The outcome measures to be considered include: • angioedema attacks (including frequency, severity, location and duration) • attack-free period • time to first attack • need for acute treatment • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
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. 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. Costs will be considered from an NHS and Personal Social Services perspective. 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:** Berotralstat for preventing recurrent attacks of hereditary angioedema (2021) NICE technology appraisal guidance 738. Lanadelumab for preventing recurrent attacks of hereditary angioedema (2019) NICE technology appraisal guidance 606. **Related technology appraisals in development:** Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over (2025) NICE technology appraisal guidance ID6394. Publication expected August 2025.

References

1. NHS Clinical commissioning: plasma derived C1-esterase inhibitor for prophylactic treatment of HAE (2016). Accessed August 2025

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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.

4. Commissioned treatment options for patients with Hereditary Angioedema secondary to C1 esterase inhibitor deficiency (HAE-C1-INH). Accessed August 2025 hereditary-amd-acquired-angioedema-algorithms.pdf