NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Donidalorsen for preventing hereditary angioedema attacks in people 12 years and over ID6457

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of donidalorsen within its marketing authorisation for preventing 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.[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), preventive (prophylactic) treatments and acute treatments. 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.

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) • Attenuated androgens • Antifibrinolytics • 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. Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over (2025) NICE technology appraisal guidance ID6284. Publication expected December 2025.

Questions for consultation

Where do you consider donidalorsen will fit into the existing care pathway for the prevention of hereditary angioedema attacks?

Would donidalorsen be used to prevent recurrent attacks or to treat acute attacks of hereditary angioedema?

Please select from the following, will donidalorsen be:

A. Prescribed in primary care with routine follow-up in primary care
B. Prescribed in secondary care with routine follow-up in primary care
C. Prescribed in secondary care with routine follow-up in secondary care
D. Other (please give details):

For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.

Are there any subgroups of people in whom donidalorsen is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Would donidalorsen be a candidate for managed access?

Do you consider that the use of donidalorsen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which donidalorsen will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation)

References

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