NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Berotralstat for preventing acute attacks of hereditary angioedema

Final scope

Draft remit/appraisal objective

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

Background

Hereditary angioedema (HAE) is an rare genetic disorder, associated with the deficiency of the protein C1-esterase inhibitor, which is a regulator of inflammatory pathways. Normally, C1-esterase inhibitor controls the enzyme cascade reactions so that uncontrolled swelling of the subcutaneous and submucosal tissues do not occur. In patients with HAE, at 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 usually occur in the mouth, the gut (affecting the submucosal tissues) and the airway, causing difficulty with breathing (with potential asphyxia) and severe pain in the stomach. The swellings can also occur in the deep tissues of the skin (affecting the dermis and subcutaneous tissues) causing significant impact, for example if the hands, feet or genitals are affected.

Most angioedema attacks are associated with trauma, medical procedures, emotional stress, menstruation, oral contraceptive use, infections, or the use of medications such as ACE inhibitors. Attacks are unpredictable; severity and frequency of previous attacks do not predict severity and frequency of future attacks. Attacks usually last approximately 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 defined by low levels of a normal protein C1-esterase inhibitor in the plasma.
- type II is defined by normal level of a dysfunctional protein C1-esterase inhibitor in the plasma.
- type III is not a result of the deficiency of protein C1-esterase inhibitor. However, it is known that oestrogen has a role not yet fully understood[2].

It is estimated that HAE affects between 1 per 50,000 to 1 per 100,000 of the population[1]. Most cases develop in childhood and some cases develop in early adulthood. HAE usually occurs during the first 10 to 20 years of life.

There are 3 approaches to managing HAE: avoidance of factors that trigger HAE (e.g. minor trauma, hormone replacement therapy), acute treatments and preventive (prophylactic) treatments of acute attacks. Short-term preventive treatments aim to prevent an attack before known triggers for example, dental work or surgery. Long-term preventative treatments are used routinely to reduce the need for treatment of acute attacks. As a long-term strategy, attenuated androgens (such as danazol) or C1-esterase inhibitor (C1-INH) such as Cinryze or Berinert can be used. Danazol

does not have a marketing authorisation in the UK for HEA. Anti-fibrinolytics, such as tranexamic acid, can also be used. Icatibant, Berinert, Cinryze and Ruconest can be used for treating acute attacks.

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.

The technology

Berotralstat (Orladeyo, BioCryst Pharmaceuticals) is a potent oral synthetic inhibitor of protein kallikrein. It is administered orally

Berotralstat does not currently have a marketing authorisation in the UK for preventing acute attacks of HAE. It is currently being studied in a clinical trial in people aged 12 years and older with HAE to prevent acute attacks compared with placebo.

Intervention	Berotralstat
Population	People aged 12 years and older with hereditary angioedema
Comparators	Established clinical management for preventing attacks of hereditary angioedema which may include: • C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest) attenuated androgens and anti-fibrinolytics (Berinert and Ruconest do not currently have a marketing authorisation in the UK for routine prevention of attacks) • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy
Outcomes	The outcome measures to be considered include: • angioedema attacks (this includes frequency, severity, location and duration) • need for acute treatment • mortality • adverse effects of treatment • health-related quality of life.

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 technologies 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 and NICE Pathways	**Related Technology Appraisals:** Lanadelumab for preventing recurrent attacks of hereditary angioedema (2019). NICE Technology Appraisal 606. Review date October 2022. **Related NICE Pathways:** Immune system conditions (2016) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 105. NHS England (2016) Clinical Commissioning Policy: Plasma derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/16045_FINAL.pdf Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 to 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

1 NHS Clinical commissioning: plasma derived C1-esterase inhibitor for prophylactic treatment of HAE (2013). Accessed March 2020 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/16045_FINAL.pdf

2 Amanda Rodrigues Miranda APFdU, Dominique Vilarinho Sabbag, Wellington de Jesus Furlani, Patrícia Karla de Souza, Osmar Rotta. Hereditary angioedema type III (estrogen-dependent) report of three cases and literature review. An Bras Dermatol. 2013;88(4):578–84.

