NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Eplontersen for treating polyneuropathy caused by hereditary transthyretin amyloidosis

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of eplontersen within its marketing authorisation for treating polyneuropathy caused by hereditary transthyretin amyloidosis.

Background

Hereditary transthyretin amyloidosis affects people born with inherited mutations in the transthyretin (TTR) gene. This causes the liver to produce abnormal transthyretin protein (ATTR) which accumulates as deposits in the tissues of the body (ATTR amyloid deposits) and causes amyloidosis. These accumulated deposits can disrupt the structure and damage the function of the affected tissues. Most commonly deposits accumulate in the peripheral nervous system (polyneuropathy) or in the tissues of the heart (cardiomyopathy). Over time, these deposits can cause symptoms of polyneuropathy (such as pain, loss of sensation and weakness in the hands, arms, legs or feet) and symptoms of cardiomyopathy (such as chest pain, shortness of breath and fluid overload). In some cases, the autonomic nervous system which controls involuntary body functions such as blood pressure, heart rate, and digestion, may also be affected by amyloidosis.

The condition is progressive. Based on polyneuropathy disability score it can be classified into 4 stages (Coutinho et al. 1980).[1] Stage 0 denotes asymptomatic disease, people with stage 1 disease have mild symptoms and can walk, people with stage 2 disease have moderate symptoms and require assistance to walk, and people with stage 3 disease have severe symptoms and need to use a wheelchair or are bedbound. The effects and complications of the disease can lead to death within 5 to 15 years of symptoms developing.

The prevalence of hereditary ATTR amyloidosis is estimated to be less than 1 in 100,000 people in the general European population.[2] In the UK there are thought to be around 230 people with the disease.[3]

Current treatment options for people with polyneuropathy caused by hereditary ATTR amyloidosis include symptom relief and supportive care including pain management, nutritional and mobility support and mitigation of the effects of the disease on other organs.

- Vutrisiran is recommended for treating hereditary ATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy (NICE technology appraisal 868).
- Patisirian is recommended for treating hereditary ATTR amyloidosis in adults with stage 1 and stage 2 polyneuropathy (NICE highly specialised technologies guidance 10).

- Inotersen is recommended for treating stage 1 and stage 2 polyneuropathy in adults with hereditary ATTR amyloidosis (NICE highly specialised technologies guidance 9).

Diflunisal is a non-steroidal anti-inflammatory drug which makes transthyretin less likely to form amyloid accumulations. It is sometimes used outside of its marketing authorisation to treat hereditary ATTR amyloidosis. It is contraindicated in people with cardiac impairment and those taking anticoagulants.

Liver transplantation, which prevents the formation of additional amyloid deposits by removing the main source of abnormal transthyretin production, is an option for some people with a specific genetic mutation. However, this mutation is uncommon in England, and transplantation can only take place early in the course of the disease, so it is very rarely used in England.

The technology

Eplontersen (brand name unknown, AstraZeneca) does not currently have a marketing authorisation in the UK for hereditary ATTR amyloidosis.

It has been studied in a randomised clinical trial and compared with inotersen in adults with hereditary ATTR amyloidosis who have polyneuropathy stage 1 or 2.

Intervention(s)	Eplontersen
Population(s)	Adults with polyneuropathy caused by hereditary ATTR amyloidosis.
Comparators	• Vutrisiran • Patisiran • Inotersen
Outcomes	The outcome measures to be considered include: • overall survival • neurological impairment • symptoms of polyneuropathy • cardiac function • autonomic function (including the effects on the gastrointestinal system and postural hypotension) • weight loss • effects of amyloid deposits in other organs and tissues (including the eye) • serum transthyretin • motor function • 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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. 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:** Vutrisiran for treating hereditary transthyretin-related amyloidosis (2023) NICE Technology Appraisal 868. Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (2021) NICE Technology Appraisal 696. Patisiran for treating hereditary transthyretin-related amyloidosis (2019) NICE Highly Specialised Technology 10. Inotersen for treating hereditary transthyretin-related amyloidosis (2019) NICE Highly Specialised Technology 9 **Ongoing technology appraisals:** Tafamidis for treating transthyretin amyloidosis with cardiomyopathy ID6327
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England Manual for prescribed specialised services, service 46: Diagnostic service for amyloidosis (adults), March 2023. NHS England Highly specialised services 2019/20: diagnostic service for amyloidosis. 2022 NHS England standard contract for diagnostic service for amyloidosis (all ages). 2013/14.

Questions for consultation

Where do you consider eplontersen will fit into the existing care pathway for hereditary ATTR amyloidosis?

- Are there differences between vutrisiran, patisiran and inotersen used for hereditary ATTR amyloidosis in terms of patient use?
- Which treatment(s) have a substantial market share?
- Which treatment(s) are part of established clinical practice?
- Is inotersen a relevant comparator based on use in practice?
- How clinically similar would eplontersen be considered to vutrisiran and patisiran?

How distinct or similar are the current clinical pathways for polyneuropathy and cardiomyopathy caused by hereditary ATTR amyloidosis?

- Should people with polyneuropathy who also have symptoms of cardiomyopathy be considered separately?
- Would tafamidis for treating transthyretin amyloidosis with cardiomyopathy (subject to NICE guidance) be a relevant comparator for eplontersen?

Would eplontersen be a candidate for managed access?

Do you consider that the use of eplontersen 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 the treatment 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 is considering evaluating this technology through its cost comparison evaluation process.
Please provide comments on the appropriateness of appraising this topic through this 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).

Technologies can be evaluated through the cost-comparison process if they are expected to provide similar or greater health benefits, at a similar or lower cost, compared with technologies that have been previously recommended (as an option) in published NICE guidance for the same indication. Companies can propose cost-comparison topics to NICE at any stage during topic selection and scoping. NICE will route technologies for evaluation through the cost-comparison process if it is agreed during scoping that the process is an appropriate route to establish the clinical and cost effectiveness of the technology.

NICE's health technology evaluations: the manual states the methods to be used where a cost comparison case is made.

- Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators?
- Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe.
- Will the intervention be used to treat the same population as the comparator(s)?
- Overall is the technology likely to offer similar or improved health benefits compared with the comparators?
- Would it be appropriate to use the cost-comparison methodology for this topic?

References

1. Coutinho PD, Lima JL, Barbosa AR. 1980. Forty years of experience with type I amyloid neuropathy: review of 436 cases In: Glenner GG, de Freitas AF, editors. Amyloid and amyloidosis. Amsterdam: Excerpta Medica; p. 88-98.

2. Orpha.net. 2022 Prevalence of rare diseases: Bibliographic data.

3. National Institute for Health and Care Excellence (NICE). 2023. Resource impact report: Vutrisiran for treating hereditary transthyretin related amyloidosis (TA868).