**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Health Technology Evaluation**

# Vutrisiran for treating hereditary transthyretin-related amyloidosis

**Draft scope**

## Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of vutrisiran within its marketing authorisation for treating hereditary transthyretin-related amyloidosis.

## Background

Hereditary transthyretin-related amyloidosis (hATTR) affects people born with inherited mutations in the transthyretin gene. This causes the liver to produce abnormal transthyretin protein which accumulates as deposits in the tissues of the body (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 or in the tissues of the heart. 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 and the neuropathy can be classified into 4 stages. Stage 0 denotes asymptomatic disease: people with stage I disease have mild symptoms and can walk, people with stage II disease have moderate symptoms and require assistance to walk, and people with stage III 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 hATTR amyloidosis is estimated to be less than 1 in 100,000 people in the general European population[1]. In the UK there are thought to be around 150 people with the disease.

Current treatment options for people with hATTR 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. Patisirian is recommended for treating hATTR amyloidosis in adults with stage 1 and stage 2 polyneuropathy (HST10). Inotersen is recommended for treating stage 1 and stage 2 polyneuropathy in adults with hATTR amyloidosis (HST 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 hATTR 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**

Vutrisiran (AMVUTTRA, Alnylam Pharmaceuticals) is an RNA interference (RNAi) therapeutic that inhibits the production of disease-causing transthyretin (TTR) protein by the liver, leading to a reduction in the level of TTR in the blood. It is administered by subcutaneous injection.

Vutrisiran does not currently have a marketing authorisation in the UK for polyneuropathy caused by hATTR. It has been studied in a phase III clinical trial compared with patisiran for people with polyneuropathy caused by hereditary transthyretin amyloidosis.

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| **Intervention(s)** | Vutrisiran |
| **Population(s)** | People with hereditary transthyretin-related amyloidosis. |
| **Comparators** | Established clinical management without vutrisiran including:<br>• Inotersen<br>• Patisiran |
| **Outcomes** | The outcome measures to be considered include:<br>• Overall survival<br>• neurological impairment<br>• symptoms of polyneuropathy<br>• cardiac function<br>• autonomic function (including the effects on the gastrointestinal system and postural hypotension)<br>• weight loss<br>• effects of amyloid deposits in other organs and tissues (including the eye)<br>• serum transthyretin<br>• motor function<br>• mortality<br>• adverse effects of treatment<br>• 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.<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>• Costs will be considered from an NHS and Personal Social Services perspective. |

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| **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>Inotersen for treating hereditary transthyretin amyloidosis (2019). NICE Highly specialised technologies guidance (HST 9). Review date 2022<br>Patisiran for treating hereditary transthyretin amyloidosis (2019). NICE Highly specialised technologies guidance (HST 9). Review date 2022 |
| **Related National Policy** | NHS England Manual for prescribed specialised services, service 46: Diagnostic service for amyloidosis (adults), 2017/18. https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf<br>NHS England standard contract for diagnostic service for amyloidosis (all ages), 2013/14.<br>https://www.england.nhs.uk/wp-content/uploads/2013/06/e13-diag-serv-amyloidosis.pdf<br>The NHS Long Term Plan, 2019. NHS Long Term Plan<br>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) |

**Questions for consultation**

Have all relevant comparators for vutrisiran been included in the scope? Which treatments are considered to be established clinical practice in the NHS for hereditary transthyretin-related amyloidosis:

- Are inotersen and patisiran relevant comparators?
- Are other experimental treatments such as doxycycline plus tauroursodeoxycholic acid comparators?
- Are there any other treatments that should be included as comparators?
- Which treatments are considered to be established clinical practice in the NHS for hATTR amyloidosis?
- What does having an adequate polyneuropathy disability score translate to in terms of the stages of neuropathy?
- Are there any subgroups of people in whom vutrisiran is expected to be more clinically effective and cost effective or other groups that should be examined separately, for example, people who have stage 3 and 4 polyneuropathy?

Are the outcomes listed appropriate?

- Is serum transthyretin a relevant outcome?
- Which elements of autonomic function are affected by the condition and might be improved by vutrisiran?

- Would vutrisiran have an effect on cardiomyopathy outcomes?

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 vutisiran 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.

- Do you consider vutrisiran to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

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

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. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on NICE's health technology evaluation processes is available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).

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

- Would it be appropriate to use the cost-comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

**References**

1. Orpha.net. Prevalence of rare diseases. Bibliographic data (June 2022). https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf