NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Tafamidis for treating transthyretin amyloid cardiomyopathy

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of tafamidis within its marketing authorisation for treating transthyretin amyloid cardiomyopathy for national commissioning by NHS England.

Background

Transthyretin amyloidosis (ATTR) is caused by abnormal transthyretin (TTR) proteins being produced by the liver and accumulating as deposits in the tissues of the body (amyloidosis)[1]. Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of transthyretin amyloidosis in which most deposits accumulate in the heart[1], causing the heart tissue to thicken and stiffen[2]. There are two causes of ATTR-CM:

- Wildtype ATTR-CM (also known as senile systemic amyloidosis or senile cardiac amyloidosis) mostly affects older individuals and more men than women[2]. Median survival is 3.6 years for people with wildtype ATTR[3];

- Hereditary ATTR-CM (also known as familial amyloid cardiomyopathy[2]) affects people born with inherited mutations in the TTR gene[2]. These variants are thought to be less stable than the wildtype and so are more likely to form amyloid fibrils[2]. Reported median survival is 2.1 years following diagnosis for Val122Ile variant[3], one of the most prevalent TTR variants in the UK[4].

Symptoms of ATTR-CM can include shortness of breath, palpitations and abnormal heart rhythms, most frequently atrial fibrillation or atrial flutter, ankle swelling, fatigue, fainting and chest pain. ATTR-CM is a progressive disease with symptoms usually starting after the age of 60 years[1]. Death in most people with ATTR-CM is from sudden death and progressive heart failure[1].

The prevalence of ATTR-CM in the UK is currently unknown. It is difficult to reliably estimate due to potential under-diagnosis and under-reporting of the condition[4,5]. In the UK there are thought to be around 600 people with wildtype ATTR-CM and 200 people with hereditary ATTR-CM. Hospital episode statistics for 2016/2017 recorded a total of 1,473 finished consultant episodes, 1,077 admissions and 612 day cases for organ-limited amyloidosis of any type[7].

Current treatment options for ATTR-CM are limited and mainly focus on symptom management and supportive care. Patisiran and inotersen have marketing authorisations for treating hereditary transthyretin related amyloidosis. The marketing authorisations state that the technologies should be used in people with polyneuropathy, but many people with polyneuropathy as a result of transthyretin amyloidosis also have cardiomyopathy. Both technologies are currently being evaluated by NICE. Liver transplantation, which prevents the formation of additional amyloid deposits by removing the main source of abnormal transthyretin production, or heart transplantation, are options for some people with ATTR-CM and 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

Tafamidis (Vyndaqel, Pfizer) binds to transthyretin (TTR) in the blood. This binding stabilises the shape of TTR and prevents the formation of misfolded proteins. In turn, this then stops the formation of amyloids. Tafamidis is taken orally.

Tafamidis does not currently have a marketing authorisation in the UK for the treatment of transthyretin amyloid cardiomyopathy. It has been studied in a clinical trial for ATTR-CM (wildtype or hereditary) and additional safety data is being collected as part of a long-term extension study. Tafamidis has a marketing authorisation in the UK for the treatment of transthyretin familial amyloid polyneuropathy (TTR-FAP) in people with stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment.

Intervention(s)	Tafamidis
Population(s)	People with transthyretin amyloid cardiomyopathy
Comparators	People with wildtype ATTR-CM: • Established clinical management without tafamidis People with hereditary ATTR-CM: • Established clinical management without tafamidis • Patisiran (subject to ongoing NICE evaluation) • Inotersen (subject to ongoing NICE evaluation)

Outcomes	The outcome measures to be considered include: • mortality • cardiac function • cardiovascular-related hospitalisation • cardiovascular-related mortality • transthyretin stabilisation • 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 and NICE Pathways	Appraisals in development: Inotersen for treating hereditary transthyretin-related amyloidosis. NICE Highly Specialised Technology ID1242. Publication date: TBC Patisiran for treating hereditary transthyretin-related amyloidosis. NICE Highly Specialised Technology ID1279. Publication date: TBC
Related National Policy	NHS England Manual for prescribed specialised services, service 46: Diagnostic service for amyloidosis (adults), September 2018.

	https://www.england.nhs.uk/publication/manual-for-prescribed-specialised-services/ NHS England standard contract for diagnostic service for amyloidosis (all ages), 2013/14. https://www.england.nhs.uk/wp-content/uploads/2013/06/e13-diag-serv-amyloidosis.pdf NHS England (2018) Highly specialised services 2017 Department of Health and Social Care (2018) The UK Strategy for Rare Diseases. Second Progress Report from the UK Rare Diseases Policy Board Department of Health (2016) The UK Strategy for Rare Diseases. Rare Diseases implementation plan for England Department of Health (2013) The UK strategy for rare diseases Welsh Government (2017) Rare diseases implementation plan

Questions for consultation

How is transthyretin amyloid cardiomyopathy diagnosed in the NHS? Are there any differences in how wildtype and hereditary ATTR cardiomyopathy are diagnosed?

- If a specific treatment for this condition became available, is the number of people diagnosed expected to increase?

Following diagnosis, how is transthyretin amyloid cardiomyopathy managed? Please answer separately for wildtype and hereditary ATTR cardiomyopathy if appropriate.

- Is the disease managed at local centres?

How long would treatment with tafamidis be expected to continue for in clinical practice?

Which treatments are considered to be established clinical practice in the NHS for treating transthyretin amyloid cardiomyopathy? Please answer separately for wildtype and hereditary ATTR cardiomyopathy if appropriate.

- Would some of the people eligible for treatment with patisiran and inotersen be eligible for treatment with tafamidis (and vice versa)?
- Are heart or liver transplantation relevant comparators?
- Are there any other treatments that should be included specifically as comparators?

Are the outcomes listed appropriate? Please answer separately for wildtype and hereditary ATTR cardiomyopathy if appropriate.

- Are there any other outcomes that should be included?

Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

Where do you consider tafamidis will fit into the treatment pathway for treating transthyretin amyloid cardiomyopathy?

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 tafamidis 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.

Do you consider tafamidis 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 tafamidis can result in any potential significant and 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 Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which 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. Maurer MS, Elliott P, Merlini G, Shah SJ, Cruz MW, Flynn A, et al. Design and Rationale of the Phase 3 ATTR-ACT Clinical Trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). Circ Heart Fail. 2017 Jun;10(6). Available from: https://www.ahajournals.org/doi/10.1161/CIRCHEARTFAILURE.116.003815 [Accessed 12 November 2018]

2. Ruberg FL, Berk JL. Transthyretin (TTR) Cardiac Amyloidosis. Circulation. 2012;126(10):1286-300. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501197/ [Accessed 12 November 2018]

3. Maurer MS, Grogan DR, Judge DP, Mundayat R, Packman J, Lombardo I, et al. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stabilization and clinical outcomes. Circulation: Heart Failure. 2015:CIRCHEARTFAILURE. 113.000890. Available from: https://doi.org/10.1161/CIRCHEARTFAILURE.113.000890 [Accessed 12 November 2018]

4. Patel K, Hawkins P. Cardiac amyloidosis: where are we today? Journal of internal medicine. 2015;278(2):126-44. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26077367 [Accessed 12 November 2018]

5. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. European Heart Journal. 2015;36(38):2585-94

6. University College London - Centre for Amyloidosis and acute phase proteins. Amyloidosis Overview. 2018. Available from: https://www.ucl.ac.uk/amyloidosis/national-amyloidosis-centre/amyloidosis-overview [Accessed 12 November 2018]

7. NHS Digital. Hospital Admitted Patient Care Activity, 2016-17. 2017. Geographic coverage: England, Data collection period: Dataset downloaded: Available from: http://digital.nhs.uk/catalogue/PUB22378 [Accessed June 2018]