NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Tafamidis for treating transthyretin amyloid cardiomyopathy

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of tafamidis within its marketing authorisation for treating transthyretin amyloid cardiomyopathy.

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 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]. The most prevalent TTR variants in the UK are Val112Ile and T60A[4]. The Val122Ile variant is mostly associated with isolated cardiomyopathy without neuropathy. Reported median survival is 2.1 years following diagnosis for people with the Val122Ile variant[3] and 3.4 years for people with the T60A variant[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 70 years in people with wildtype ATTR-CM or after the age of 60 years in people with the Val112Ile and T60A variants of hereditary ATTR-CM[5]. 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[5,6]. In the UK there are thought to be around 600 people with wildtype ATTR-CM and 200 people with hereditary ATTR-CM. The number of new diagnoses made each year, in particular for wildtype ATTR-CM, is increasing rapidly, in part due to the wider availability of non-invasive diagnostic tests.

Current treatment options for ATTR-CM are limited and mainly focus on symptom management and supportive care such as diuretics. A small proportion of people with cardiomyopathy as a result of transthyretin amyloidosis also have polyneuropathy (that is, they have a mixed phenotype). Inotersen is recommended as an option for treating stage 1 and stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis (HST9). Patisiran is currently being evaluated by NICE as a Highly Specialised Technology (HST). 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 abnormal 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 (ATTR-CM)
Comparators	People with ATTR-CM: • Established clinical management without tafamidis People with mixed phenotype transthyretin amyloidosis (that is, people presenting with both transthyretin familial amyloid polyneuropathy [TTR-FAP] and hereditary ATTR-CM): • Patisiran (subject to ongoing NICE evaluation) • Inotersen

Outcomes	The outcome measures to be considered include: • overall survival • cardiovascular-related mortality • cardiac function (such as global longitudinal strain or brain natriuretic peptide [BNP] level) • cardiovascular-related hospitalisation • functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • 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 and subsequent treatment technologies will be taken into account.
Other considerations	If the evidence allows, the following subgroups will be considered: • severity of heart failure (such as by New York Heart Classification class) 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: Inotersen for treating hereditary transthyretin-related amyloidosis. (2019) NICE Highly Specialised Technology 9. Appraisals in development:

	Patisiran for treating hereditary transthyretin-related amyloidosis. NICE Highly Specialised Technology ID1279. Publication expected August 2019.
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), 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

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