NICE National Institute for Health and Care Excellence

NICE guidance

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA696.

1 Recommendations

1.1 Tafamidis is recommended, within its marketing authorisation, as an option for treating wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in adults. Tafamidis is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

ATTR-CM is a progressive condition that can lead to heart failure, but treatment options are limited to managing symptoms and best supportive care. Tafamidis is the first treatment for ATTR-CM that aims to treat the condition.

Evidence from the main clinical trial shows that tafamidis reduces deaths and hospitalisations from conditions affecting the heart and blood vessels compared with placebo. But it is uncertain how long people live when having tafamidis and how long they take it for. Longer-term evidence from a different study reduces this uncertainty.

The most likely cost-effectiveness estimate for tafamidis is within the range that NICE considers an acceptable use of NHS resources. So, tafamidis is recommended.

2 Information about tafamidis

Marketing authorisation indication

2.1 Tafamidis (Vyndaqel, Pfizer) is indicated for 'the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for tafamidis.

Price

2.3 The list price is £10,685 for 30 capsules of 61 mg tafamidis (excluding VAT; BNF online, accessed April 2024).

2.4 The company has a commercial arrangement. This makes tafamidis available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Transthyretin amyloidosis (ATTR) is caused by abnormal transthyretin proteins being produced by the liver and accumulating as deposits in tissues of the body (amyloidosis). Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a type of ATTR in which most deposits accumulate in the heart. There are 2 types of ATTR-CM:

- Wild-type ATTR-CM, which is more common. It mostly affects older people and is more common in men.
- Hereditary ATTR-CM (also known as familial amyloid cardiomyopathy), which affects people born with inherited mutations in the transthyretin gene.

The clinical experts explained that ATTR-CM is a progressive, life limiting and debilitating condition. For wild-type ATTR-CM, symptoms usually start in people aged 70 and over. For hereditary ATTR-CM, symptoms usually start in people aged 60 and over. It can cause shortness of breath, palpitations and abnormal heart rhythms such as atrial fibrillation or atrial flutter, ankle swelling, fatigue, fainting and chest pain. The clinical experts noted that death in most people with ATTR-CM is from sudden death and progressive heart failure.

Burden of disease

3.2 As ATTR-CM progresses it can lead to the loss of mobility and independence.

This affects quality of life for people with ATTR-CM and their carers because people become increasingly reliant on carers to do daily activities. In turn, carers may experience fatigue and isolation as they devote more time to caring. The patient expert explained that ATTR-CM substantially affects physical ability, noting that walking even short distances can be challenging. There is an associated financial burden because people, or their carers, may have to retire earlier than expected or travel long distances to specialist treatment centres. Delays in diagnosis can also cause anxiety for people living with symptoms without fully understanding what they are experiencing. In hereditary ATTR-CM, multiple family members can be affected, which can carry considerable psychological burden, such as anxiety and guilt about passing the condition on to children. The committee concluded that ATTR-CM is a debilitating condition that substantially affects both physical and psychological wellbeing.

Clinical management

Diagnosis

3.3 The clinical experts noted that the diagnosis pathway has changed since the ATTR-ACT trial was done (see section 3.5). They explained that most diagnoses are now made using medical imaging, rather than biopsy, and the condition is diagnosed at earlier stages in more people. But the clinical experts noted that ATTR-CM remained undiagnosed in many people. The patient expert also highlighted that even with the improved diagnosis, without any disease-modifying treatments, early diagnosis is of limited value to people living with ATTR-CM. The committee noted that while the rate of diagnosis of ATTR-CM has increased rapidly, the condition is still likely to be underdiagnosed.

Comparators

3.4 The company considered that the most appropriate comparator for tafamidis in this indication is best supportive care (BSC). This is limited to the management of symptoms as well as supportive care, such as diuretics. A small number of people with ATTR-CM also have polyneuropathy with mixed clinical features. NICE's final

scope for this evaluation included treatments for mixed phenotype ATTR as comparators. NICE has recommended 3 treatments for polyneuropathy. See:

- NICE's technology appraisal guidance on vutrisiran for treating hereditary ATTR
- NICE's highly specialised technologies guidance on inotersen for treating hereditary ATTR
- NICE's highly specialised technologies guidance on patisiran for treating hereditary ATTR.

The company did not include these treatments as comparators in its submission because they had not been evaluated or licensed for ATTR-CM. The committee noted that the marketing authorisation for tafamidis did not specifically mention polyneuropathy. It acknowledged that, because it is rare for people to have both ATTR-CM and polyneuropathy, there would not be enough evidence to consider it separately. So, the committee agreed that vutrisiran, inotersen and patisiran could not be considered appropriate comparators. The final scope also included diflunisal as part of established clinical management without tafamidis. But the company had excluded diflunisal as a comparator because it is not licensed for ATTR-CM and there is no randomised controlled trial evidence for its use. Clinical experts stated that people with a recent diagnosis of ATTR-CM no longer have diflunisal because it is not well tolerated. The NHS England submission also stated people only have diflunisal for end-stage disease, and tafamidis is used at earlier disease stages. The committee agreed that diflunisal is not an appropriate comparator. The clinical experts noted that sodium-glucose co-transporter-2 (SGLT2) inhibitors have shown benefits in quality of life and survival in observational studies in people with ATTR-CM, but they are not part of established NHS practice in England. They also commented it was likely that tafamidis would be used alongside SGLT2 inhibitors. So, the committee agreed that SGLT2 inhibitors are not an appropriate comparator for tafamidis. The committee concluded that BSC was the only appropriate comparator.

Clinical effectiveness

Clinical-effectiveness evidence

3.5 In the original NICE technology appraisal guidance on tafamidis for treating ATTR-CM (from here referred to as TA696), the company gave evidence from 2 trials:

- ATTR-ACT (pivotal): a 30-month, phase 3 double-blind randomised controlled trial. It evaluated how effective, safe, and tolerable tafamidis was compared with placebo in adults with wild-type or hereditary ATTR-CM, who had a staging of 1 to 3 (n=441) based on the New York Heart Association (NYHA) functional classification.
- ATTR-ACT extension study (ATTR-ACT LTE): an open-label extension of ATTR-ACT including people from ATTR-ACT as well as people with ATTR-CM who did not take part in ATTR-ACT (ongoing; number of patients not reported).

  The ATTR-ACT pivotal trial randomised people to have either 80 mg tafamidis meglumine (n=176), 20 mg tafamidis meglumine (n=88) or placebo (n=177) using a ratio of 2:1:2. Everyone who had treatment in ATTR-ACT LTE had 61 mg tafamidis, or 80 mg tafamidis meglumine if 61 mg was not available. Medicines considered to be BSC were permitted alongside tafamidis, as long as these were stable for at least 4 weeks before the start of trial treatment. The committee noted that the dose of tafamidis used in ATTR-ACT was different to the dose in the marketing authorisation, which is 61 mg. But the marketing authorisation states that the relative bioavailability of 61 mg tafamidis is similar to 80 mg tafamidis meglumine at a steady state. For this evaluation, the company gave longer-term data collected from ATTR-ACT LTE with 84 months follow up (see section 3.6). The company did not present any new comparative evidence, for example, tafamidis compared with any form of BSC. The EAG noted that the company had not updated the systematic literature review for clinical-effectiveness data from TA696. The company explained that the ATTR-ACT trial and extension was the most robust data available for tafamidis. It noted that there is no real-world evidence available for tafamidis in England because it is not yet available. One of the clinical experts noted that newer real-world evidence from observational studies in

France, Japan and the US supports the results of the ATTR-ACT trial and extension. The committee concluded that it would have preferred to see an updated systematic literature review for clinical-effectiveness data. But it noted the comments from clinical experts that newer observational data supported the results of the ATTR-ACT trial and extension. So, the committee concluded that the clinical evidence given in this evaluation was suitable for decision making.

Longer-term data from ATTR-ACT LTE

3.6 The company gave new clinical effectiveness and safety evidence from the August 2021 data cut of ATTR-ACT LTE with 84 months of follow up. The company gave updated overall survival (OS) and time-to-treatment discontinuation (TTD) data for tafamidis only, which was censored for heart transplant, cardiac mechanical assist device (CMAD) implantation, and loss to follow up. The exact figures are considered commercial in confidence by the company and cannot be given here. The company also provided all-cause mortality data for people in NYHA class 1 and 2 compared with people in NYHA class 3, and adverse events from the longer-term follow up. The committee noted that the other trial outcomes that were specified in the scope, including cardiovascular-related mortality and hospitalisations, had not been included in the company submission. It noted that the ClinicalTrials.gov record for ATTR-ACT LTE stated that cardiovascular-related mortality and hospitalisations were assessed at month 60. The company stated that only OS and TTD were available at 84 months and analysis for the other outcomes had not yet been carried out. The committee concluded that it would have liked to see all new data that was available since TA696 on the outcome measures specified in the scope.

Economic model

Company's modelling approach

3.7 Similar to TA696, the company modelled the costs and benefits for tafamidis using a cohort-level Markov state-transition model. To capture the natural

disease progression of ATTR-CM, model health states were based on the NYHA classification system. The model included 5 health states: 4 NYHA classes (1, 2, 3, and 4) and death. People could move to a more severe health state (decline) or to a less severe one (improve). The company did not do updated systematic literature reviews for economic evaluations, costs and resource use or utilities. The committee noted that the company used the same model structure as TA696 and considered that the company's model was suitable for decision making. It concluded that it would have preferred for the company to update its systematic literature reviews for economic evaluations, costs and resource use and utilities.

OS extrapolation

3.8 In TA696, the committee preferred the log-normal model to extrapolate OS for tafamidis. For this evaluation, the company used the longer-term data from ATTR-ACT LTE to fit parametric survival extrapolations for OS for tafamidis. The company's preferred OS extrapolation for tafamidis was the generalised gamma model. The company explained that the non-parametric hazard profiles from ATTR-ACT LTE showed a clear peak at around 2 years, followed by a decline. It noted that only the log-logistic, log-normal and generalised gamma models are able to predict a local peak hazard as seen in the trial and that the generalised gamma model had the closest agreement with the non-parametric hazard estimators. The generalised gamma model also showed high goodness of fit to the observed data from ATTR-ACT LTE, because it had the lowest Akaike information criterion (AIC) value of all the candidate parametric survival models. The EAG highlighted that although the AIC value was low, the generalised gamma model had a higher Bayesian information criterion value than the log-normal model, which suggests a worse fit to the observed data. The generalised gamma model also predicted the highest long-term survival estimates for tafamidis of all the candidate parametric survival models. The committee noted that OS at 20 years for people having tafamidis predicted by the company's preferred generalised gamma model was relatively high, given that the average cohort age would be around 95 years at this time point. The exact survival rate is considered commercial in confidence by the company so cannot be reported here. The committee questioned the clinical plausibility of using the generalised gamma model. The company confirmed that survival estimates were capped to general population life tables. The committee noted that the choice of extrapolation

model for OS did not have a large effect on the cost-effectiveness results. It concluded that it preferred to use the log-normal model to extrapolate OS for tafamidis, because it appeared to fit the observed data better and had more plausible long-term survival estimates than the generalised gamma model. In its response to draft guidance consultation, the company updated its base case to include the log-normal model and align with the committee's preferred assumption.

Treatment effect after stopping tafamidis

3.9 The EAG noted that, after the observed trial period, the company assumed that an increasing number of surviving people stopped having tafamidis but continued to have sustained treatment benefit without gaining any further treatment costs. It considered that this assumption was unlikely to be clinically plausible. The EAG base case included the same assumption but also gave 2 scenarios:

- No further stopping of tafamidis after the observed trial period with continued treatment benefit and costs.
- People continuing to stop tafamidis after the observed trial period, with costs applied only to people still having tafamidis. Transition probabilities, adverse event rates, cardiovascular-related hospitalisations, survival and utilities for the BSC group were applied to people who stopped tafamidis, from the point that they stopped.

  The clinical experts explained that once treatment with tafamidis is stopped, the transthyretin protein in the blood would revert to its normal behaviour and begin to form amyloid deposits. So, they considered that it is not plausible that there would be continued treatment effect after stopping tafamidis. They explained that in people who stopped treatment it was not known whether:

- amyloid formation would happen at the same rate as people who had not had tafamidis, but from a lower starting level of amyloid deposition, or
- there would be a 'catch-up effect' observed, so amyloid formation would happen at a higher rate than in people who had not had tafamidis.

The clinical experts also noted that they would not expect an immediate return to BSC outcomes in people who stopped treatment. The company highlighted that the observed 84-month data from ATTR-ACT LTE given in the company submission included both people who had tafamidis and those who had stopped treatment. So, it stated that its base case did not assume an indefinite treatment effect after tafamidis was stopped. The company highlighted a figure that it believed shows that the EAG's second scenario substantially underpredicts the observed OS and TTD from ATTR-ACT LTE. The committee noted that the OS and TTD data given by the company was censored for heart transplant, CMAD implantation and loss to follow up. The clinical experts noted that tafamidis would be stopped after having a heart transplant but would be continued after CMAD implantation. The clinical experts stated that they would expect stopping treatment to continue after the observed trial period, so the committee concluded that the EAG's first scenario was not appropriate for decision making. The company's base case assumed a sustained treatment effect without sustained treatment costs. The committee recalled its conclusion in TA696 that it was overly optimistic to assume continued benefit after stopping tafamidis, without a cost. It considered that given the mechanism of action of tafamidis, it was implausible that there would be a sustained treatment effect after stopping treatment, and for this reason thought the company's base case was too optimistic. But given the uncertainty, the committee concluded at the first committee meeting that the second EAG scenario was the most appropriate for decision making.

3.10 In response to the draft guidance consultation the company provided an updated approach to modelling treatment discontinuation in its base case. This removed people who stopped treatment from the tafamidis OS extrapolation and applied the mean survival rate from the ATTR-ACT BSC trial arm to people who stopped tafamidis. This removed the high hazard of death for those who stopped tafamidis in the EAG's second scenario. It also separated out people who continued treatment, and prevented double-counting the risk of death for people who stopped treatment. The company also explained that the EAG's second scenario was not supported by the ATTR-ACT LTE data. The EAG generally agreed with this updated approach and accepted it as its preferred approach. It stated that ideally a tunnel state could be used to track the time until treatment is

stopped, which would allow an OS curve specific for people who stopped treatment to be created. The EAG highlighted that using the company's new approach with a constant mean hazard likely underestimated OS in the first years and overestimated it in the later years. It was unsure if this accurately reflected what would happen in practice. The company suggested that the initial underestimation could offset some of the uncertainty. The committee was satisfied that the company's updated base case reflected outcomes for people who stopped treatment, and preferred to use this approach in its decision making.

Utility values compared with UK age-matched average

3.11 In the company submission the utility values for people in NYHA class 1 (in both tafamidis and BSC arms) and class 2 (tafamidis arm) were higher than the UK general population age-matched average. The exact utility values are considered commercial in confidence by the company and cannot be given here. The company considered that people in NYHA class 1 typically do not have symptoms and physical activity limitations, and people in NYHA class 2 only experience slight difficulties with physical activity. But the general population of the same age may have other conditions that affect their quality of life. The committee noted that the starting age in the economic model was 74 years. The EAG base case included capped utility values to the age-matched equivalent. The clinical experts explained that it was not plausible that someone with ATTR-CM would have a better quality of life than someone of a similar age from the general population. So, the committee concluded that capped utility values for the NYHA class 1 and NYHA class 2 health states were appropriate for decision making. In its response to draft guidance consultation, the company updated its position to align with the committee's preferred approach and applied a cap on health state utility values that were above the average value for the general population of the same age.

Treatment dependency of utility values

3.12 In TA696, the committee concluded that BSC values (treatment-independent) and utility values should be applied for the NYHA class 4 health state because:

- there was a substantial difference in utility values between arms in NYHA class 4, while utility values for tafamidis and BSC in the other NYHA classes were similar, and
- NYHA class 4 utility values were based on a low number of observations.

The company stated in its submission and in the committee meeting that it had applied treatment-independent utility values in the NYHA class 4 health state. But in its response to clarification questions from the EAG, it stated that people having tafamidis in the NYHA class 4 health state would have the utility value for tafamidis from ATTR-ACT and would only be assigned the utility value for BSC after stopping treatment. The EAG preferred to use the same utility values for the tafamidis and BSC arms for NYHA class 4, for people having treatment as well as for those who stopped. The committee considered the treatment-dependent utility values applied for NYHA health states 1 to 3 and noted that for some health states the tafamidis value was higher, but in other health states the BSC value was higher. The committee asked what the clinical justification was for this and whether scenarios had been done applying treatment-dependent utility values for all health states. The company said it did not have scenarios exploring this. The committee heard the concerns raised about the reliability of the treatment-dependent values for NYHA class 4 and concluded that using BSC utilities was more appropriate for decision making. The committee would have also preferred to see a decision for using treatment-dependent utility values for NYHA health states 1 to 3 and scenarios exploring treatment-dependent utility values for all health states. In its response to draft guidance consultation, the company updated its base case to use BSC utility values for NYHA class 4.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio (ICER)

3.13 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS

resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted that:

- there are currently no disease-modifying treatments available for ATTR-CM in England, so there is substantial unmet need in this population (see section 3.4)
- the company had given 84-month follow-up data for people having tafamidis, but no new comparative data was available since TA696 (see section 3.6)
- there is uncertainty about the outcomes for people who stopped treatment with tafamidis, but the company's updated approach was reasonable (see section 3.9).

The committee agreed that an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Cost-effectiveness estimates

3.14 The company's cost-effectiveness estimates are considered to be commercial in confidence by the company so cannot be reported here. The company's and the EAG's updated base case, which included an updated commercial arrangement, estimated that the deterministic and probabilistic ICERs for tafamidis compared with BSC were within the range normally considered a cost-effective use of NHS resources. The company's and EAG's revised base case included the following assumptions:

- using a log-normal parametric distribution to model OS for tafamidis (see section 3.8)
- applying a cap on health state utility values above the general population age-matched average for NYHA class 1 and 2 for tafamidis and BSC (see section 3.11)
- using BSC values for NYHA class 4 instead of treatment-dependent utility

values (see section 3.12)

- censoring the people who stopped treatment from the tafamidis OS extrapolation and using the mean survival rate from the ATTR-ACT BSC arm for people who stopped treatment (see section 3.9).

The committee concluded that the company's and EAG's base-case ICER included its preferred assumptions. This ICER was within the range NICE considers an acceptable use of NHS resources. So, it concluded that tafamidis is recommended.

Other factors

Equality

3.15 The committee noted comments from the clinical and patient experts that hereditary ATTR-CM disproportionally affects people with certain genetic variants (such as Val122Ile), which are more prevalent in African Caribbean and Hispanic ethnic groups. In these populations, ATTR-CM is often diagnosed later and has worse outcomes than in other people with ATTR-CM. Val122Ile is not associated with polyneuropathy so people with this variant do not have access to disease-modifying therapy. The professional group submissions also highlighted the fact that prescribing tafamidis might be restricted to specialist centres and that people with ATTR-CM are often older and could experience difficulties with travelling long distances to have treatment. The committee took these factors into account in its decision making but agreed that this was not something that could be addressed in its recommendation.

Conclusion

Tafamidis is recommended

3.16 The committee noted that there are no disease-modifying treatments for

ATTR-CM available in England and acknowledged the substantial unmet need in this population. It also noted that there is uncertainty about the outcomes in people who have stopped treatment with tafamidis, but that the company's updated approach was reasonable. So, an acceptable ICER based on this set of assumptions would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The cost-effectiveness estimate that included the committee's preferred assumptions was within the range that NICE considers an acceptable use of NHS resources. So, tafamidis is recommended.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. Because tafamidis has been available through the early access to medicines scheme, NHS England and integrated care boards have agreed to provide funding to implement this guidance 30 days after publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has wild-type or hereditary transthyretin amyloidosis with cardiomyopathy and the healthcare professional responsible for their care thinks that tafamidis is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien
Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

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