NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Review proposal of tafamidis for treating transthyretin amyloidosis with cardiomyopathy (TA696)

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (TA696) was published in 2021.

Proposal / Decision

1.TA696 should be reevaluated.

Rationale

2. A major uncertainty in this evaluation was the long-term overall survival estimates. Further follow up data published since the original evaluation indicates that survival is improved with tafamidis for people with transthyretin amyloidosis with cardiomyopathy (ATTR-CM), to a greater extent than considered during the original evaluation.

   There are a number of uncertainties which cannot be resolved, including outcomes after treatment discontinuation which had a moderate impact on the incremental cost-effectiveness ratios during the original appraisal.

   However, it is unclear what impact the updated clinical data would have on the cost effectiveness results, including those for the full population included in the marketing authorisation and relevant subgroups specified in the scope. Therefore, it is appropriate to reevaluate tafamidis for treating ATTR-CM.

Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

3.Uncertain. Pfizer indicated in email to NICE (3 July 2023) that tafamidis would have a new value proposition but no details are included on the commercial pricing list. A Patient Access Scheme would have applied if tafamidis was recommended in 2021.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

4.No

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Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

5. A number of uncertainties were identified in the original guidance:

    1. Measuring transthyretin amyloidosis with cardiomyopathy (ATTR-CM) severity using the New York Heart Association (NYHA) classification: the NYHA is a patient-reported measure which may be influenced be factors other than the disease and may vary from day to day. The committee acknowledged that there was insufficient trial data to consider an alternative objective measure as cardiac markers were not measured frequently enough in the ATTR-ACT pivotal trial or extension study (TA696 section 3.6).

    2. Reduction in diagnosis times when tafamidis implemented: company proposed during the original appraisal that the availability of tafamidis would result in ATTR-CM being detected earlier because of increased awareness. The committee concluded that there was not enough evidence provided to support the assumption that introducing tafamidis would reduce ATTR-CM diagnosis delays. It also concluded that it was highly uncertain whether any additional cost savings or quality of life benefits resulting from earlier diagnosis could be attributed to tafamidis (TA696 section 3.8).

    3. Uncertainty in effectiveness for different subgroups: for outcomes of all cause mortality and hospitalisation, worse outcomes were reported for people with hereditary ATTR-CM than wild-type ATTR-CM. For outcomes of cardiovascular-related mortality and cardiovascular hospitalisations, worse outcomes were seen for people whose disease was classed NYHA 3 than for those whose disease was classed as NYHA 1 or 2.

        The committee agreed that the subgroup results added a degree of uncertainty but accepted that the analyses were underpowered and therefore the subgroup results were not suitable for decision making (TA696 section 3.11).

    4. Continued treatment benefit following discontinuation is unclear because the mechanism of action of tafamidis is unknown. There was therefore uncertainty around the appropriate assumption to include in the model around continued treatment benefit analysis (TA696 sections 3.15 and 3.16).

    5. Overall survival in the model comes from extrapolated data from the observed trial period: the committee concluded that the company's approach to extrapolation was not fully justified and therefore only

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considered the log-normal extrapolation in decision making (TA696 section 3.17).

Points 1, 2 and 4 are unlikely to be resolved through a revaluation. This is because no further evidence has been identified which will provide further information on these uncertainties.

Points 3 and 5 may be addressed by further follow up data from the ATTR-ACT trial.

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Point 3: uncertainty in effectiveness for different subgroups

Summary

The longer term follow up from the long-term extension study of the pivotal trial used in TA696 indicates better mortality outcomes than those considered during the original evaluation for people with disease classed as NYHA 1 or 2, and NYHA 3 and for people with hereditary ATTR-CM and wild-type ATTR-CM

Subgroup	All-cause mortality tafamidis versus placebo HR (95% CI)	
	TA696	Recent follow up data (Elliot et al. 2022/23)
NYHA 1 or 2	0.57 (0.36 to 0.90)	0.50 (0.35 to 0.73)
NYHA 3	0.84 (0.54 to 1.30)	0.64 (0.41 to 0.99)
Hereditary ATTR-CM	0.69 (0.41 to 1.17)	0.57 (0.33 to 0.99)
Wild-type ATTR-CM	0.71 (0.47 to 1.05)	0.61 (0.38 to 0.82)

Detail

The evidence available from the ATTR-ACT trial during the evaluation for TA696 had 30 months follow up data for the outcome for all-cause mortality. For people with disease classed as NYHA 1 or 2, tafamidis was statistically significantly more effective than placebo for reducing all-cause mortality (HR 0.57 [95% CI 0.36 to 0.90]). No statistically significant difference between tafamidis and placebo in all-cause mortality was seen for people with disease classed as NYHA3 (HR 0.84 [95% CI 0.54 to 1.30]). For people with hereditary ATTR-CM, there was no statistically significant difference between tafamidis and placebo for all-cause mortality (HR 0.690 [95% CI 0.408 to 1.167]). For people with wild-type ATTR-CM, there was also no statistically significant difference between tafamidis and placebo for all cause mortality (HR 0.706 [95% CI 0.474 to 1.052]).

A recent study (Elliot et al. 2023) provides 60 month follow up data for people given tafamidis and 56 month follow up data for people given placebo and reports all-cause mortality by NYHA subgroup. For people with disease classed as NYHA class 1 or 2, tafamidis was statistically significantly more effective than placebo for reducing all-cause mortality (HR 0.50 [95% CI 0.35 to 0.73]). For people with disease classed as NYHA class 3, tafamidis was also statistically significantly more effective than placebo for reducing all-cause mortality (HR 0.64 [95% CI 0.41 to 0.99]).

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Another recent study (Elliot et al. 2022) provides median follow up of 58.5 months for people given tafamidis and 57.1 months for people given placebo for the outcomes of all-cause mortality. For people with hereditary ATTR-CM, tafamidis was statistically significantly more effective than placebo for reducing all-cause mortality (HR 0.57 [95% CI 0.33 to 0.99]). For people with wild-type ATTR-CM, tafamidis was also statistically significantly more effective than placebo for reducing all-cause mortality (HR 0.61 [95% CI 0.38 to 0.82]).

Point 5: overall survival in the model comes from extrapolated data from the observed trial period

Summary

The longer term follow up from the long-term extension study of the pivotal trial used in TA696 indicates better mortality outcomes than those considered during the original evaluation for the full trial population. This suggests that the long-term extrapolation of overall survival may estimate better long-term benefit with tafamidis than considered in the original evaluation.

	All-cause mortality tafamidis versus placebo HR (95% CI)	
	TA696	**Recent follow up data (Elliot et al. 2022/23)**
Full population considered for decision making in TA696	0.64 (0.47 to 0.85)	0.59 (0.44 to 0.79)

Detail

As noted above, the observed period from the pivotal trial during the original evaluation of TA696 was 30 months. There was also additional data from a long-term extension study which was available for the outcome of all-cause mortality for the full trial population. At an average of 36 months follow up, tafamidis was statistically significantly more effective than placebo for reducing all-cause mortality (HR 0.64 [95% CI 0.47 to 0.85]).

A recent study (Elliot et al. 2022) provides median follow up of 58.5 months for people given tafamidis and 57.1 months for people given placebo for the outcomes of all-cause mortality. Tafamidis was statistically significantly more effective than placebo for reducing all-cause mortality (HR 0.59 [95% CI 0.44 to 0.79]).

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This longer term follow up from the long-term extension study of the pivotal trial used in TA696 indicates better mortality outcomes than those considered during the original evaluation for the full trial population.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

6. There is unlikely to be any implications of related NICE guidance on the existing guidance.

The following NICE guidance is relevant to this evaluation:

- Inotersen for treating hereditary transthyretin-related amyloidosis (2019) NICE Highly Specialised Technology 9.
- Patisiran for treating hereditary transthyretin-related amyloidosis (2019) NICE Highly Specialised Technology 10.
- Vutrisiran for treating hereditary transthyretin-related amyloidosis (2023) NICE Technology Appraisal 868.

All 3 of these evaluations recommend treatment for people with hereditary transthyretin-related amyloidosis in adults with stage 1 or stage 2 polyneuropathy.

Inotersen (HST9) and patisiran (HST10) were considered as comparators in the original evaluation. The committee noted that it is rare for people to have ATTR-CM and polyneuropathy and therefore there would not be enough evidence to consider this subgroup separately. It concluded that inotersen and patisiran could not be considered as comparators to tafamidis. Given this reasoning, it is likely that there would also be insufficient evidence to consider vutisiran as a comparator, which has been published since TA696.

Equality issues

7. The equalities issues raised were addressed in the Final Appraisal Document. The committee agreed that none of the issues could be addressed by a technology appraisal.

The following issues were raised:

- ATTR-CM disproportionally affect people from certain ethnic family backgrounds.
- There are inconsistencies levels of awareness of the types of ATTR-CM which can lead to variations in diagnosis delays.
- Older people with ATTR-CM would be denied access to tafamidis while younger people would be able to access tafamidis through the Early Access to Medicines Scheme.

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- Prevalence of ATTR-CM in women may be underestimated.

Proposal/decision paper sign off

Linda Landells – Associate Director, Technology Appraisals and Highly Specialised Technologies

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Contributors to this paper

Information Specialist: Paul Levay

Technical Analyst: Albany Chandler

Associate Director: Linda Landells

Project Manager: Kate Moore

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