IQWiG Reports – Commission No. A20-101

# Tafamidis (transthyretin amyloid polyneuropathy) –

## Benefit assessment according to §35a Social Code Book V[1]

**Extract**

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Tafamidis (Transthyretin-Amyloidose mit Polyneuropathie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| ATTR | transthyretin amyloidosis |
| ATTR-PN | transthyretin amyloid polyneuropathy |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |

# 2 Benefit assessment

## 2.1 Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tafamidis. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 November 2020.

### Research question

The aim of the present report is the assessment of the added benefit of tafamidis in comparison with patisiran as appropriate comparator therapy (ACT) in adult patients with transthyretin amyloidosis (ATTR) and stage 1 symptomatic polyneuropathy.

Table 2: Research question of the benefit assessment of tafamidis

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| 1 | Transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment | Patisiran[b, c] |

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in the study arms, taking into account the special features of the disease hereditary transthyretin amyloidosis, and is documented as concomitant treatment.
c. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

### Results

Overall, the company did not present any data for the present research question of the benefit assessment.

The company identified no study of direct comparison for the present research question. For this reason, the company searched for studies for an indirect comparison. The studies with tafamidis (study B3461020) and with patisiran (study APOLLO) identified by the company, each in comparison with placebo, are not suitable for an indirect comparison in the view of the company, as the similarity of the target populations is not given.

**Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]**

As the company did not present any data for the assessment of the added benefit of tafamidis in comparison with patisiran in adult patients with ATTR and symptomatic stage 1 polyneuropathy, an added benefit of tafamidis is not proven.

Table 3 shows a summary of probability and extent of the added benefit of tafamidis.

Table 3: Tafamidis – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment | Patisiran[b, c] | Added benefit not proven |

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in the study arms, taking into account the special features of the disease hereditary transthyretin amyloidosis, and is documented as concomitant treatment.
c. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

**Supplementary note**

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2011, where the G-BA had determined a minor added benefit of tafamidis. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

## 2.2 Research question

The aim of the present report is the assessment of the added benefit of tafamidis in comparison with patisiran as ACT in adult patients with ATTR and stage 1 symptomatic polyneuropathy.

Table 4: Research question of the benefit assessment of tafamidis

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| 1 | Transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment | Patisiran[b, c] |

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in the study arms, taking into account the special features of the disease hereditary transthyretin amyloidosis, and is documented as concomitant treatment.
c. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

## 2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tafamidis (status: 15 October 2020)
- bibliographical literature search on tafamidis (last search on 15 October 2020)
- search in trial registries/trial results databases for studies on tafamidis (last search on 15 October 2020)
- search on the G-BA website for tafamidis (last search on 15 October 2020)
- bibliographical literature search for the ACT (last search on 15 October 2020)
- search in trial registries/trial results databases for the ACT (last search on 15 October 2020)
- search on the G-BA website for the ACT (last search on 15 October 2020)

To check the completeness of the study pool:

- bibliographical literature search on tafamidis (last search on 3 December 2020)

No relevant study of direct comparison was identified from the check. The company also identified no relevant study of direct comparison between tafamidis and patisiran.

As no study of direct comparison was available for the present benefit assessment, the company aimed for an indirect comparison. The company identified 2 RCTs in its search: one study with tafamidis and one study with patisiran, each in comparison with placebo (study B3461020 [3], study APOLLO [4]).

From the point of view of the company, an indirect comparison on the basis of these 2 studies is not possible, as the 2 studies show insufficient similarity of the target populations on the basis of the available patient characteristics with regard to disease stage, existing mutation, age, sex ratio and pretreatment at baseline. Thus, the identified studies did not meet the basic requirements for a methodologically sound indirect comparison.

In addition, the company referred to the publication Samjoo (2020) [5]. According to the company, this study assessed the heterogeneity of the 2 studies, B3461020 and APOLLO, and found the studies unsuitable for conducting indirect comparisons of therapies with tafamidis and patisiran in patients with transthyretin amyloid polyneuropathy (ATTR-PN).

Overall, the company did not present any data for the present research question and derived no added benefit. Therefore, the approach of the company is not commented on.

## 2.4 Results on added benefit

The company did not present any data on the comparison of tafamidis with the ACT. Thus, there is no hint of an added benefit of tafamidis in comparison with patisiran in adult patients with ATTR and symptomatic stage 1 polyneuropathy. An added benefit is therefore not proven.

## 2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of tafamidis in comparison with the ACT is summarized in Table 5.

Table 5: Tafamidis – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment | Patisiran[b, c] | Added benefit not proven |

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in the study arms, taking into account the special features of the disease hereditary transthyretin amyloidosis, and is documented as concomitant treatment.
c. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above concurs with that of the company.

The G-BA decides on the added benefit.

**Supplementary note**

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2011, where the G-BA had determined a minor added benefit of tafamidis. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

**References for English extract**

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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*The full report (German version) is published* under *https://www.iqwig.de/en/projects/a20-101.html*.