Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Tafamidis (New Therapeutic Indication: Amyloidosis in Cardiomyopathy)

of 20 August 2020

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, Nos. 2 and 3 SGB V in conjunction with Chapter 5, Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last twelve calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medicinal benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (*cf* Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment of the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient tafamidis was listed for the first time on 15 December 2011 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 17 February 2020, tafamidis received the marketing authorisation for a new therapeutic indication ("Vyndaqel® is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)") classified as a major type 2 variation according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 24 February 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient tafamidis with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

Tafamidis for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit is assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 2 June 2020 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-03) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 through 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tafamidis.

1 General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of tafamidis (Vyndaqel ®) in accordance with the product information

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

2.1.2 Extent of the additional benefit and the significance of the proof

In summary, the additional benefit of tafamidis is assessed as follows:

For adult patients with wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM), there is a hint for a considerable additional benefit.

Justification:

The benefit assessment is based on the randomised, placebo-controlled, double-blind, multi-centre ATTR-ACT Phase III pivotal study ATTR-ACT (B3461028) conducted to investigate the efficacy and safety of tafamidis in patients with hereditary or wild-type ATTR-CM under standard therapy.

The study included 441 adult patients with ATTR-CM (NYHA classes I–III) diagnosed by biopsy and histological detection of amyloid deposits. The study population was stratified by TTR genotype (hereditary or wild type) and severity disease (NYHA class I or NYHA classes II + III) and randomised to the treatment arms tafamidis meglumine (80 mg; n = 176), tafamidis meglumine (20 mg; n = 88)), and placebo (n = 177) at a ratio of 2:1:2. An initial screening phase was followed by a treatment phase of 30 months and either a follow-up of 28 days or a transition of the patients into the extension study. Patients received oral tafamidis or placebo daily, each as an add-on to an optimised, stable standard therapy for the treatment of cardiac insufficiency in the case of ATTR amyloidosis. The primary endpoint of the study was the combined endpoint overall mortality and frequency of cardiovascular hospitalisation.

The mean age of the study population was approx. 75 years. Slightly more patients in the intervention group were 75 years or older (60%) compared with the control group (49%). Almost 90% of the study participants were male. The study included significantly more patients with wild type genotype (approx. 75%). In addition, only a few NYHA Class I patients were included in the study. At the start of study, almost all of the study participants were suffering from at least one other concomitant disease. However, there were no significant imbalances between the study arms.

All patients took other medicinal products before and during the study. At baseline, 89% of patients in the tafamidis arm and 91% in the placebo arm received at least one concomitant medication. Concomitant interventions were defined as ongoing or initiated interventions at any time after baseline (day 1) until the final study round. All study participants received at least one concomitant therapy. Diuretics were most commonly used with comparable proportions in both treatment groups. A pacemaker was implanted in approximately 15% of patients in both study arms, and an implantable defibrillator in 10% of patients in the tafamidis group and in 15% of patients in the placebo group.

More patients in the control group (52%) discontinued the study than patients in the intervention group (36%). The main reason was deaths. However, more than twice as many patients in the placebo group (n = 37) were no longer willing to participate in the study compared with 17 patients in the tafamidis group. Although only five patients in both study arms discontinued the study because of organ transplant, six patients in the intervention group underwent heart transplant or combined heart and liver transplant during the study. The median observation time of the safety population was slightly longer in the tafamidis arm as was the median treatment time.

Because tafamidis at a dosage of 20 mg is not covered by the marketing authorisation for the treatment of ATTR-CM, only the study arms tafamidis 80 mg and placebo will be considered in the benefit assessment. In the following, the analyses submitted at month 18 are used for the walking ability morbidity endpoint and the analyses submitted at month 30 for all other endpoints.

Mortality

In the ATTR-ACT study, overall mortality was defined as the time between randomisation and death by any cause. Cardiovascular mortality was defined as the time between randomisation and death from a cardiovascular event. The following events were considered to be cardiovascular events: cardiac insufficiency, arrhythmia, myocardial infarction, sudden cardiac death, stroke, and other cardiovascular causes that are not among the events listed but which nevertheless have a specific cause (e.g. pulmonary embolism, peripheral arterial disease, vascular disease, peripheral embolism, venous thrombosis, or other vascular causes or complications). For the primary analysis of this endpoint, according to the study documentation, a study discontinuation because of heart transplant, combined heart/liver transplant, or implantation of a mechanical circulatory support device was assessed in the same way as the event “death”. For the sensitivity analysis, according to the study documents, patients were censored at the time of discontinuation of the study because of these events. Patients who dropped out of follow-up for other reasons (lost to follow-up) were censored at the last time they were shown to be alive. Furthermore, patients were censored if they were still alive at the time of the analysis.
In addition, analyses without censoring were submitted subsequently in the written statement procedure. In these, patients with heart transplant, combined heart/liver transplant, or implantation of mechanical circulatory support were not censored before their death but continued to be monitored over the duration of the study. The analyses without censoring are considered to be the more adequate analyses for the benefit assessment and are subsequently considered as the main analyses for the mortality endpoints.

For the analyses of overall mortality, the deaths that occurred in the ATTR-ACT study were classified according to cardiovascular cause. The total number of deaths was lower (n = 49; 28%) under treatment with tafamidis than under placebo (n = 72; 41%). The proportion of cardiovascular deaths in the total number of deaths was comparable between treatment groups. Patients in the tafamidis arm underwent heart transplant or combined heart/liver transplant or mechanical circulatory support more frequently (4.5%) than patients in the control group (2.3%). The median observation period (30 months) was comparable in both treatment arms. Different analyses were carried out depending on the cardiovascular cause of the deaths as well as the evaluation of patients with transplants and implants. Within the mortality category, the benefit assessment primarily focuses on overall mortality, which includes deaths from all causes and also uses the uncensored analyses submitted with comments.

The median survival was not achieved in any of the study arms. There is a statistically significant benefit in the overall mortality endpoint in favour of tafamidis therapy. There was no interaction in the sub-groups for the endpoint overall mortality.

For the cardiovascular mortality additionally considered, the analyses of cardiovascular mortality also included deceased patients as events for which the cardiovascular cause was "undetermined". From the analyses in which patients with heart transplants or combined heart/liver transplants or implants of mechanical circulatory support devices were not censored before their death, but rather continued to be observed over the duration of the study, a statistically significant effect in favour of tafamidis can be derived for the additionally considered endpoint "cardiovascular mortality".

Morbidity

Hospitalisations

In the ATTR-ACT study, hospitalisation was defined as any non-selective admission to an acute care hospital for medical treatment that resulted in an inpatient stay of at least 24 hours or overnight. The number of hospitalisations and the cause were surveyed by the study centre at each study round.

71% of patients in the tafamidis group and 77% in the control group experienced at least one hospitalisation during the study. To analyse the frequency, the annual rate of any hospitalisation was calculated from the respective number of hospitalisations per patient and the years under observation. The adjusted rates (using Poisson regression) resulted in a statistically significant rate ratio in favour of tafamidis in the frequency of all hospitalisations. In the primary analyses, missing values were not replaced.

Interaction tests showed an effect modification for the frequency of any hospitalisation by the characteristic NYHA classification (Class I + II vs Class III). In the sub-group NYHA Class I + II, there was a statistically significant treatment effect in favour of tafamidis. This effect was reversed in the NYHA Class III sub-group to the disadvantage of tafamidis. However, the disadvantage is not statistically significant.

In the overall view, the hospitalisations at month 30 result in a statistically significant advantage for tafamidis. However, this is relativised by the existing effect modification by the characteristic NYHA classification (class I + II vs class III). Patients with NYHA Class III did not benefit in the hospitalisation endpoint. As already discussed by the EMA[2] and in the oral hearing of clinical experts, this leads to uncertainties regarding the benefit of treatment with tafamidis in later stages of the disease.

Walking ability (6MWT)

In the ATTR-ACT study, performance was assessed using the 6-minute walk test (6MWT). The 6MWT was developed to measure functional physical abilities or physical fitness. This is a standardised and established test procedure that is used for diagnosis and follow-up in a variety of indications. In the ATTR-ACT study, the implementation of the 6MWT was standardised.

In the ATTR-ACT study, the walking distances in 6MWT varied greatly between patients at baseline. Because of limitations of the *post hoc* defined relevance thresholds used, the pre-

2 EPAR: https://www.ema.europa.eu/en/documents/variation-report/vyndaqel-h-c-2294-x-0049-g-epar-assessment-report_en.pdf

specified analyses of the mean change in walking distance are used for the benefit assessment.

For the analysis, all test persons whose TTR genotyping was available were considered. A survey was conducted both at baseline and post baseline. Based on this, results for 90% of patients treated with tafamidis and 86% of patients treated with placebo were included in the analysis. For the last scheduled round in month 30, results for the ITT population are available only for 57% of the tafamidis group and 40% of the control group. The return rates for all patients still alive at the time of the survey were 79% in the tafamidis group and 65% in the control group at Month 30 and 88% in the tafamidis group and 84% in the placebo group at Month 18. For the benefit assessment, the analysis of the mean change in walking distance at Month 18 is primarily used for the 6MWT because the return rates fell below 70% after Month 18. The analyses for Month 30 are considered as a support.

At Month 18, patients in the intervention group deteriorated by an average of 39 m during the study, while patients in the control group deteriorated by an average of 84 m. For the mean change in walking distance compared with baseline, there is a statistically significant advantage in favour of tafamidis (LS-MD: 45.04 m), the extent of which cannot be conclusively assessed.

For the additionally considered mean change of walking distance from baseline to Month 30, there was a statistically significant advantage in favour of tafamidis (LS-MD: 75.77 m).

Based on the ATTR-ACT study, for walking ability at Month 18, there is a statistically significant overall effect in favour of treatment with tafamidis, the extent of which cannot be conclusively assessed. This advantage is confirmed by the supportive analyses for month 30.

EQ-5D-VAS

The EQ-5D-VAS is a valid and reliable instrument for recording general health status. It has already been evaluated and used in various indications, including patients with cardiac disorders.

In the treatment arms, the return rates for EQ-5D were above 70% at all times until month 30.

For the analysis, the ATTR-ACT study included all subjects with a baseline survey and another post-baseline survey whose TTR genotyping was available. Based on this, results for 91 % of patients treated with tafamidis and 90 % of patients treated with placebo were included in the analysis. In the primary analysis, missing values were not replaced. For the benefit assessment, the analyses of the mean change of EQ-5D VAS from baseline to month 30 are used. Responder analyses to evaluate the endpoint were not submitted.

In the ATTR-ACT study, health status based on EQ-5D VAS deteriorated by 2.21 points at Month 30 compared with baseline in the intervention group and by 9.96 points in the control group. The change over the study period calculated using ANCOVA (MMRM) was −3.43 points in the tafamidis arm and −12.92 points in the placebo group. According to LS-MD, the difference at Month 30 compared with baseline is statistically significant between the treatment groups. Based on Hedges' g, the confidence interval of the effect is completely above the irrelevance threshold of 0.2. Thus, at Month 30, a clinically relevant, statistically significant benefit for tafamidis compared with placebo can be derived for health status.

In addition, two sensitivity analyses replaced missing values based on pattern mixture models. This confirmed the advantage of tafamidis at month 30 in the EQ-5D VAS. Similar to the primary analysis, both analyses showed a statistically significant effect in favour of tafamidis. This can also be assessed as clinically relevant in the analysis of the pattern mixture model 1 according to Hedges' g.

Quality of life

Kansas City Cardiomyopathy Questionnaire (KCCQ)

In the ATTR-ACT study, quality of life was surveyed using the KCCQ. The KCCQ is a disease-specific questionnaire used to assess the health-related quality of life in patients with cardiomyopathy. It is completed by the patients themselves. The last two weeks were looked at. The instrument consists of 23 items divided into six domains: Physical limitations (six items), symptoms consisting of symptom frequency and burden (seven items), symptom stability (one item), social impairment (four items), self-efficacy (two items), and quality of life (three items). The answer options are on a Likert scale of 5 to 7 points depending on the item. For evaluation, the items of the respective domains are summed and transformed to a scale from 0 to 100. Higher values correspond to a better condition. The individual domains can be summarised via their mean value to two aggregated overall values: on one hand, the KCCQ-CSS (Clinical Summary Score) consisting of the domains physical limitations and symptoms and on the other hand, the KCCQ-OSS (Overall Summary Score) consisting of the domains physical limitations, symptoms, social impairment, and quality of life. In addition to the evaluation of the KCCQ-OSS and the KCCQ-CSS, evaluations for the individual domains were also planned in the study protocol. The CSS of the KCCQ is not considered for the benefit assessment because the domains contained therein are already part of the KCCQ-OSS. The return rates for the KCCQ-OSS in the treatment arms up to month 30 were above 70% at all times.

For evaluation, the pharmaceutical company carried out post hoc time-to-event analysis for the time until the first improvement or deterioration by ≥ 5 points in the KCCQ-OSS. 105 patients (59.7%) in the intervention group deteriorated by at least 5 points in the KCCQ-OSS over the course of the study compared with 128 patients (72.3%) in the control group. The hazard ratio for the time to deterioration was statistically significant in favour of tafamidis. In the analysis of time to improvement in the KCCQ-OSS by ≥ 5 points, more patients from the tafamidis arm improved numerically. However, this effect was not statistically significant. In addition to the relevance threshold of 5 points, the pharmaceutical company also examined threshold values of 6 and 10 points for the time to deterioration or improvement in the KCCQ-OSS. For time to deterioration, the results of these analyses were statistically significant in favour of tafamidis (HR: 0.61; 95% CI: [0.46; 0.79]; p = 0.0002 and HR: 0.54; 95% CI: [0.40; 0.72]; p < 0.0001) and not statistically significant for the time to improvement (HR: 1.27; 95% CI: [0.89; 1.80]; p = 0.1895 and HR: 1.23; 95% CI: [0.82; 1.86]; p = 0.3226). The analyses were thus consistent with the results of the relevance threshold of 5 points.

In the analyses primarily submitted and presented in the benefit assessment, fluctuating values in the KCCQ-OSS were found for at least some of the test subjects. These were therefore included in the analyses as both "improved" and "worsened". In order to meet the question of the relevance of the response criterion "time to first improvement/deterioration", further time-to-event analysis on "permanent deterioration" were submitted in the written statement procedure. On the other hand, no analyses of "permanent improvement" were submitted later.

In the time-to-event analyses submitted later on, response criteria were selected to reflect the permanence of the deterioration. In the present case, the selected criterion of a deterioration in three follow-up round by at least 5 points in the KCCQ-OSS compared with baseline appears sufficient to record a relevant change in quality of life. For this operationalisation of a "permanent deterioration" of the health-related quality of life, a statistically significant effect in favour of tafamidis was shown – analogous to the first deterioration. Uncertainties result from the *post hoc* defined and unjustified operationalisation of the criterion of three subsequent dates and the still unclear reasons for censorship. With regard to the further *post hoc* defined operationalisation of a "permanent" deterioration in the KCCQ-OSS by ≥ 5 points (no improvement after deterioration), it is unclear to which persons the permanent deterioration without improvement refers in one of the follow-up rounds. This analysis is not taken into account.

In addition to the time-to-event analyses, the mean change in the KCCQ-OSS between baseline and month 30 was evaluated. The difference according to LS-MD is statistically significant between the treatment arms at Month 30 and, based on Hedges' g, can also be classified as clinically relevant. For neither the time-to-event analyses nor the evaluation of the change between baseline and Month 30 did the subgroup analyses show effect modifications.

Overall, a statistically significant, clinically relevant advantage is derived for tafamidis compared with placebo in quality of life at month 30.

Side effects

The safety analysis included all AE that occurred between receiving the first dose of the study medication and the end of study participation (TEAE). In accordance with SAP, AE were coded according to MedDRA. The safety population consists of 353 patients divided between the study arms tafamidis (N = 176) and placebo (N = 177); the safety population thus corresponds to the ITT population. The median duration of observation was largely comparable between treatment arms (30.6 months under tafamidis and 28 months under placebo). Because of this difference of 2.6 months, the pharmaceutical company carried out time-to-event analyses to evaluate the AE. Patients with no event were censored 28 days after the end of treatment or at the time of death if earlier. If the patient participated in the extension study, censoring was carried out when the double-blind treatment phase was completed. In each case, the time until the first AE occurred is included in the analysis. Number and reasons for censorship during the study could not be identified. Only 113 patients (64.2%) in the tafamidis group and 85 patients (48.0%) in the placebo group completed the study without discontinuing the study or dying prematurely.

The analyses with effect estimator RR submitted subsequently in the written statement procedure were represented as sensitivity analysis in the amendment and did not show any differences relevant to the benefit assessment compared with the analyses with HR as effect estimator.

Total rates

98.3% of patients in the tafamidis group had at least one AE compared with 98.9% in the placebo group. In neither in the time to the first severe AE nor in the SAE was there a statistically significant difference between the treatment arms. Therapy discontinuations because of AE were slightly more frequent in the control group. However, this difference was not statistically significant. Sensitivity analyses excluding all preferred terms of the system

organ class “cardiac disorders” also showed no statistically significant differences between the treatment groups. Furthermore, the subgroup analyses did not reveal any effect modifications.

Adverse events by system organ class

In detail, with regard to system organ classes, the most frequent AE occurred in the areas of “cardiac disorders”, “gastrointestinal disorders”, “infections and infestations”, and “respiratory, thoracic, and mediastinal disorders”. With an incidence ≥ 10% in one of the two treatment groups and a difference ≥ 10% between the treatment groups, the hazard ratio for the system organ classes “respiratory, thoracic, and mediastinal disorders”, “renal and urinary disorders”, and “metabolism and nutrition disorders” each shows a statistically significant difference in favour of tafamidis. In the preferred terms, with an incidence ≥ 10% in one of the two treatment groups and a difference ≥ 10% between the treatment groups, there are statistically significant differences also in favour of tafamidis between the treatment arms with respect to the hazard ratio for “dyspnoea” and “pleural effusion”. Sensitivity analyses excluding all preferred terms of the system organ class “cardiac disorders” are not available for the system organ classes and preferred terms.

For the severe AE with an incidence ≥ 5% by system organ class and preferred term in one of the two treatment groups and a difference ≥ 5% between the treatment groups, the analysis using the hazard ratio showed no statistically significant differences between the treatment arms.

During the study, about half of all patients suffered at least one SAE of the system organ class “cardiac disorders”. For SAE with an incidence of more than 5% by system organ class and preferred term in one of the two treatment groups and a difference ≥ 5% between the treatment groups, the analysis using the hazard ratio also showed no statistically significant differences between the treatment arms.

<u>Overall assessment/conclusion</u>

For the treatment of adult patients with ATTR-CM, results on mortality, morbidity, quality of life, and side effects over 30 months are available based on the pivotal Phase III ATTR-ACT RCT.

In the mortality category, there is a statistically significant advantage for overall mortality in favour of treatment with tafamidis. There is also a statistically significant advantage for tafamidis over placebo in the additionally considered endpoint “cardiovascular mortality”.

In the category of morbidity, the patient-relevant endpoint walking ability (6MWT) results in a statistically significant advantage for tafamidis, the extent of which cannot be conclusively assessed. A statistically significant, clinically relevant advantage in favour of tafamidis can also be derived for health status (EQ-5D-VAS). In addition, the morbidity endpoint “hospitalisations” is seen as an overall advantage for tafamidis. However, this is relativised by the existing effect modification by the characteristic NYHA classification (class I + II vs class III).

In the quality of life category, tafamidis has a statistically significant and clinically relevant advantage compared with placebo.

In the endpoint category side effects, the overall rates show no relevant differences between the treatment groups.

In summary, the statistically significant and clinically relevant benefits of tafamidis compared with placebo in three categories are considered to be significant overall on the basis of the

criteria in Section 5, paragraph 7 of the AM-NutzenV, taking into account the severity of the condition, the written statements, and the oral hearing.

Significance of the evidence

The ATTR-ACT study is a randomised, double-blind Phase III study with a treatment period of 30 months to assess the additional benefit in the ATTR-CM indication.
The risk of bias at the study level is estimated as low across all endpoints. At the endpoint level, the risk of bias for the endpoints on mortality and side effects is low. The bias for the other endpoints is estimated to be high.

For the endpoint “hospitalisations”, there are regional differences that can lead to a distortion of the number of hospitalisations. It is unclear whether these have been fully compensated by randomisation without stratification by country or centre. These regional differences also lead to uncertainties in the transferability of the results to the German healthcare context.

For the endpoint walking ability using 6MWT, the risk of bias is estimated to be high in relation to the evaluations for Month 18. From month 12 on, return rates varied in the treatment arms; in the tafamidis arm, these were > 5 percentage points higher than in the control arm. The bias tends to be more to the disadvantage of tafamidis but cannot be conclusively assessed in this direction.

In the endpoint health status measured using the VAS of EQ-5D, the return rates at all survey points in time were over 70% of the persons still alive at that time. Analogous to the 6MWT, the return rates in the treatment arms also varied here. Because of the decreasing return rates in the course of the study in connection with the different return rates in the treatment arms, there is a high risk of bias for this endpoint. Like the 6MWT, this is more to the disadvantage of tafamidis.

For the endpoint KCCQ-OSS there is an overall high risk of bias, caused by decreasing return rates over time as well as the uncertainties previously discussed under the endpoint description regarding the permanence and relevance of the change in quality of life. Similar to the 6MWT and the EQ5D-VAS, the bias tends to be to the disadvantage of tafamidis, although the direction of the bias cannot be conclusively assessed.

Beyond the aspects mentioned above, further uncertainties arise because of the effect modification by NYHA stage seen in the endpoint “hospitalisations”. The previously described disadvantage for patients with NYHA class III was also addressed by the regulatory authority in the EPAR. The ATTR-ACT study population also differs from the approval population (according to the product information diagnosis by scintigraphy) with regard to the indication by biopsy evidence. It remains unclear whether in clinical practice, patients with ATTR-CM indicated by scintigraphy benefit in the same way as those indicated by biopsy as was shown in the ATTR-ACT study.

In the overall view, the uncertainties described justify a downgrading of the reliability of data to a hint for an additional benefit.

2.1.3 Summary of the assessment

The present assessment refers to the benefit assessment of the medicinal product Vyndaqel® with the active ingredient tafamidis.

Tafamidis was approved as an orphan drug under “special conditions” and is indicated “for the treatment of wild type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).”

For the benefit assessment, the pharmaceutical company presents the results of the pivotal, Phase III ATTR-ACT RCT with results on mortality, morbidity, quality of life, and side effects over 30 months.

In the mortality category, there is a statistically significant advantage for overall mortality in favour of treatment with tafamidis. There is also a statistically significant advantage for tafamidis over placebo in the additionally considered endpoint “cardiovascular mortality”.

In the category of morbidity, the patient-relevant endpoint walking ability (6MWT) results in a statistically significant advantage for tafamidis, the extent of which cannot be conclusively assessed. A statistically significant, clinically relevant advantage in favour of tafamidis can also be derived for health status (EQ-5D-VAS). In addition, the morbidity endpoint “hospitalisations” is seen as an overall advantage for tafamidis. However, this is relativised by the existing effect modification by the characteristic NYHA classification (class I + II vs class III).

In the quality of life category, tafamidis has a statistically significant and clinically relevant advantage compared with placebo.

In the endpoint category side effects, the overall rates show no relevant differences between the treatment groups.

In summary, for adult patients with wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM), statistically significant and clinically relevant advantages of tafamidis compared with placebo in three categories, taking into account the strength of the results for tafamidis, a hint for a considerable additional benefit can be derived.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).
These are based on the data from the pharmaceutical company’s dossier. The figures are based on prevalence and incidence data of patients with wild type or hereditary ATTR-CM. These resulted from an analysis of data from a sample of SHI policy holders and were used in a next step to simulate the target population for 2020. The overall calculation of the number is subject to uncertainties of unknown magnitude. A tendency towards overestimation can also be assumed for the lower limit on the basis of the simulation because the mortality probability can also be higher than assumed in the simulation.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Vyndaqel® (active ingredient: tafamidis) at the following publicly accessible link (last access: 29 June 2020):

https://www.ema.europa.eu/documents/product-information/vyndaqel-epar-product-information_de.pdf

Treatment with tafamidis should be initiated and monitored only by specialists who are experienced in the treatment of patients with amyloidosis or cardiomyopathy.

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 August 2020).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Tafamidis	continuously, 1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient /treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tafamidis	61 mg	61 mg	1 × 61 mg	365	365 × 61 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Tafamidis 61 mg	30 WKA	€ 26,325.33	€ 1.77	€ 0.00	€ 26,323.56
Abbreviations: SC = soft capsules					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 August 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 24 February 2020, the pharmaceutical company submitted a dossier for the benefit assessment of tafamidis to the G-BA in due time in accordance with Chapter 5, Section 8, number 2 VerfO.

The benefit assessment of the G-BA was published on 2 June 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 23 June 2020.

The oral hearing was held on 6 July 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 11 August 2020, and the proposed resolution was approved.

At its session on 20 August 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	9 April 2019	Information of the benefit assessment of the G-BA
Working group Section 35a	30 June 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	6 July 2020	Conduct of the oral hearing
Working group Section 35a	15 July 2020 22 July 2020 5 August 2020	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 August 2020	Concluding discussion of the draft resolution
Plenum	20 August 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 August 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken