Justification

Gemeinsamer Bundesausschuss

of 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 (Re-evaluation of an orphan drug after exceeding the EUR 50 million turnover limit: amyloidosis in cardiomyopathy)

of 20 May 2021

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient tafamidis (Vyndaqel) was listed for the first time on 15 December 2011 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Vyndaqel® for the treatment of transthyretin-related amyloid polyneuropathy 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. On 17 February 2020, the medicinal product received marketing authorisation for a new indication (ATTR-CM) and was launched as a new pharmaceutical form in Germany on 1 March 2020.

In its meeting on 20 August 2020, the G-BA decided on the benefit assessment of active ingredient in the indication "Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy" in accordance with Section 35a of the German Social Code, Book V (SGB V).

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of €50 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 20 August 2020, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 December 2020, due to exceeding the €50 million turnover limit within the period from June 2019 up to and including May 2020. The pharmaceutical company submitted in due time the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 27 November 2020.

The G-BA came to a resolution on whether an additional benefit of Tafamidis compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment 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 data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tafamidis.

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

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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).

Therapeutic indication of the resolution (resolution of 20/05/2021):

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with wild-type or hereditary cardiomyopathy in transthyretin amyloidosis

Best supportive care

Best Supportive Care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. No medicinal products are explicitly authorised for the indication of treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

on 2. In principle, liver or heart transplantation can be considered as a non-medicinal treatment option in the present therapeutic indication.

on 3. A decision on the benefit assessment of new active ingredients in accordance with Section 35a of the German Social Code, Book V on tafamidis as an orphan drug is available in the present indication area with a decision dated 20 August 2020.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

In the course of the evidence search, only little evidence for the present therapeutic indication could be identified. No targeted pharmacological interventions are available for patients withwild-type or hereditary cardiomyopathy associated with transthyretin amyloidosis. Due to the very limited evidence, no standard causal therapy can be derived at present.

For the present field of application, liver or heart transplantation are basically considered as non-medicinal treatment. However, the therapeutic decision to perform a causal therapy of the underlying disease in the form of a liver and/or heart transplantation is strongly dependent on a patient-individual risk-benefit assessment and is only considered for patients who meet defined criteria regarding their degree of disease, general condition and age. It is also assumed that in the therapeutic situation in which tafamidis is considered in the present therapeutic indication, liver transplantation and/or heart transplantation is not an option for the patients. Accordingly, these procedures are not included in the appropriate comparator therapy. Therefore, according to the current product information, tafamidis should be discontinued in patients receiving liver transplantation, it is assumed that liver transplantation is not an option at the time of therapy with Tafamidis.

Although the concomitant treatment of polyneuropathy (PN) in ATTR amyloidosis is not the primary focus in the present indication, it is assumed that all patients suffering from polyneuropathy in addition to ATTR CM will also receive adequate treatment of this.

Overall, the G-BA considers it appropriate to designate best supportive care as the appropriate comparator therapy. Best Supportive Care is defined as the therapy that

provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

2.1.3 Extent and probability of the additional benefit

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 an indication of a considerable additional benefit.

Justification:

The benefit assessment is based on the randomised, placebo-controlled, double-blind, multicentre Phase III registration study ATTR-ACT to investigate the efficacy and safety of tafamidis in patients with hereditary or wild-type ATTR-CM receiving standard therapy.

The ATTR-ACT study is a multicentre, double-blind, 3-arm RCT comparing two different doses of tafamidis, each as an add-on to BSC, with placebo + BSC. Tafamidis was available as tafamidis meglumine in a dosage of either 80 mg or 20 mg. Since 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 are considered in the benefit assessment.
The study included 441 adult patients with ATTR-CM (New-York Heart Association (NYHA) classes I-III) diagnosed by biopsy and histological evidence of amyloid deposits. Patients had to be able to walk at least 100 m in the 6-minute walk test (6MWT), and the heart failure had not to be classified in NYHA class IV. The study population was randomised stratified by TTR genotype (hereditary or wild-type) and disease severity (NYHA class I or NYHA class II + III) in a 2:1:2 ratio to the tafamidis meglumine (80 mg; n = 176), tafamidis meglumine (20 mg; n = 88)), and placebo (n = 177) treatment arms. An initial screening phase was followed by a 30-month treatment phase, followed by a 28-day follow-up or transition of patients into the 60-month extension study, in which all patients received tafamidis regardless of their initial allocation. Patients received daily oral administration of tafamidis or placebo, each as an add-on to optimised, stable standard therapy for the treatment of heart failure in ATTR amyloidosis. As a primary endpoint, the study examined the combined endpoint of overall mortality and frequency of cardiovascular-related hospitalisations.

The average age of the study population was aprox. 75. 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 (approximately 75%). About 2 thirds of the patients had NYHA class II heart failure, and about 1 third had NYHA class III heart failure. A small proportion (less than 10%) of patients had NYHA class I heart failure. Patients with NYHA class IV heart failure were not included in the study.

In each case, treatment with tafamidis or placebo was in addition to symptomatic concomitant therapy, which included, for example, treatment of heart failure with concomitant drug therapies. Heart and/or liver transplantation as well as insertion of mechanical circulatory

support was possible but resulted in therapy discontinuation, and only vital status and transplantation status were queried up to month 30. However, this affected only a few patients (6 [3.4%] organ transplants and 2 [1.1%] implantations of mechanical circulatory support in the tafamidis arm vs 5 [2.8%] organ transplants in the placebo arm). It is assumed that transplantation was not an option for the other patients at the time of therapy with tafamidis.

In the following, the analyses for month 30 are used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall mortality

In the ATTR-ACT study, overall mortality was defined as the time from randomisation to death from any cause. Cardiovascular mortality was defined as the time between randomisation and death from a cardiovascular event. The following events were considered cardiovascular events: Heart failure, arrhythmia, myocardial infarction, sudden cardiac death, stroke, and other cardiovascular causes that are not listed events but still have a specific cause (e.g., pulmonary embolism, peripheral arterial disease, vascular disease, peripheral embolism, venous thrombosis, or other vascular cause or complication). For the primary analysis of both endpoints (overall mortality and cardiovascular mortality), study discontinuation due to heart transplantation, combined heart-liver transplantation, or implantation of mechanical circulatory support was considered the same as the event "death" according to the study documents.

In the analysis used by the G-BA, patients who discontinued the study due to heart transplantation, combined heart-liver transplantation or mechanical circulatory support are included in the analysis with their actual vital status (2. Sensitivity analysis of the pU. For both mortality endpoints). Therefore, contrary to the main analysis presented, the time of study termination is not included as an event (death) or censored for either endpoint in the analysis. Median survival was not achieved in any of the study arms. There was a statistically significant benefit in the endpoint overall mortality in favour of tafamidis therapy.

For the additionally considered cardiovascular mortality, a statistically significant effect in favour of tafamidis can be derived.

Morbidity

Hospitalisations (total)

In the ATTR-ACT study, hospitalisations were defined as any non-elective 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 recorded by the study centre at each study visit.

At least one hospitalisation occurred during the study in 71% of patients in the tafamidis group and in 77% in the control group. The difference is not statistically significant. For frequency analysis, the annual rate of any hospitalisation was calculated from the respective number of hospitalisations per patient and years under observation. From the adjusted rates (using

Poisson regression), there was a statistically significant rate ratio in favour of tafamidis in the incidence of any hospitalisations.

Interaction tests revealed an effect modification by the characteristic NYHA classification (class I + II vs class III) for the frequency of any hospitalisations. In the NYHA class I + II subgroup, there was a statistically significant treatment effect in favour of tafamidis. This effect was reversed in the NYHA class III subgroup to the disadvantage of tafamidis, but the disadvantage is not statistically significant.

In the overall analysis, there is a statistically significant advantage for Tafamidis in the hospitalisations at month 30, which is, however, relativised by the existing effect modification by the characteristic NYHA classification (class I + II vs class III). Patients with NYHA stage III do not benefit in the hospitalisations endpoint. As already discussed by the EMA[2] as well as in the oral hearing of clinical experts, this results in uncertainties regarding the benefit of a therapy with tafamidis in later stages of the disease.

Walking ability by means of 6MWT

Performance was assessed in a standardised manner in the ATTR-ACT study using the 6-minute walk test (6MWT). The 6MWT is designed to measure functional physical ability or physical fitness. It is a standardised and established test procedure that is used for diagnostics and progress monitoring in a variety of indications.

For the benefit assessment, analyses of the mean change in walking distance are taken into account in the same way as for the initial procedure. For the endpoint resilience, at month 30 compared to baseline, the mean change in walking distance for the main analysis results from the mixed model with repeated measures (MMRM) showed a statistically significant benefit in favour of tafamidis + BSC over placebo + BSC (LS-MWD: 75.77 m), the extent of which cannot be conclusively assessed.

The potential for bias in the results of the 6MWT at month 30 is considered high. The reason for this is a high proportion of patients with missing values or a large difference in missing values between the study arms (21% tafamidis + BSC vs 35% placebo + BSC). The additional sensitivity analyses with alternative replacement strategies cannot eliminate the high risk of bias, but confirm the robustness of the effect at month 30.
The proportion of patients with missing values by month 18 is lower than at month 30 (15% tafamidis + BSC vs 25% placebo + BSC). This analysis at month 18 provides a potentially unbiased estimate of the treatment effect due to the higher return rates, but unlike the results at month 30, it does not cover the entire course of the study. For this reason, the present benefit assessment focuses primarily on the results at month 30.

Overall, on the basis of the ATTR-ACT study, there is a statistically significant effect on walking ability at month 30 in favour of treatment with tafamidis, the extent of which cannot be conclusively assessed.

Health status (deterioration EQ-5D-VAS)

The EQ-5D-VAS is a valid and reliable instrument for assessing general health status that has been evaluated and used in various indications, including patients with heart disease.

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

Response rates for the EQ-5D were above 70% at each time point in the treatment arms through month 30. Analyses of mean change in EQ-5D-VAS from baseline to month 30 will be used for the benefit assessment. Responder analyses evaluating the endpoint were not provided.

The difference after LS-MWD at month 30 compared to baseline is statistically significant between treatment groups. Based on Hedges' g, the 95% confidence interval of the effect is completely above the irrelevance threshold of 0.2, so that at month 30 a clinically relevant, statistically significant advantage for tafamidis over BSC in health status is derived.

Quality of life

Kansas City Cardiomyopathy Questionnaire (KCCQ)

Quality of life was assessed in the ATTR-ACT study using the KCCQ. The KCCQ is a disease-specific questionnaire to assess health-related quality of life in patients with cardiomyopathy, which is completed by the affected patients themselves. The previous two weeks are considered. The instrument consists of 23 items divided into 6 domains: physical limitations (6 items), symptoms consisting of symptom frequency and burden (7 items), symptom stability (1 item), social impairment (4 items), self-efficacy (2 items), and quality of life (3 items). The response 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 up and transformed to a scale from 0 to 100. Higher values correspond to a better condition. The individual domains can be summarised by their mean value to two aggregated total values: on the one hand to the KCCQ-CSS (Clinical Summary Score), consisting of the domains physical limitations and symptoms, and on the other hand to the KCCQ-OSS (Overall Summary Score): consisting of the domains physical limitations, symptoms, social impairment and quality of life. In the study protocol, evaluations for the individual domains were planned in addition to the evaluation of the KCCQ-OSS and the KCCQ-CSS. The CSS of the KCCQ is not considered for the benefit assessment because the domains it contains are already part of the KCCQ-OSS. Response rates for the KCCQ-OSS were above 70% at all time points in the treatment arms through month 30.

As a result, in addition to the analyses of the mean change in the KCCQ-OSS, the pharmaceutical company also submitted event time analyses for the time until the (first) deterioration by ≥ 5 points in the KCCQ-OSS, as well as analyses of the 15% scale range with the submission, only the responder analyses are used for the benefit assessment.
According to IQWiG's current methodological approach (Methods 6.0, published on 5.11.20201), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for *post hoc* analyses of exactly 15% of the scale range) to be necessary for patient-reported outcomes in order to represent a noticeable change with sufficient certainty. The G-BA has already recognised a response threshold of ≥ 5 points as a clinically relevant change in KCCQ-OSS in the present indication. Therefore, against the background of the current methodological discussion and both the responder analysis with a response threshold of 15% (here ≥ 15 points) and the responder analysis with a response threshold of ≥ 5 points, presented after the written statement procedure are used to assess the additional benefit. The methodological discussion on the further procedure in the G-BA has not yet been concluded.

For the endpoint health-related quality of life, the time to worsening by ≥ 5 points in the KCCQ-OSS shows a statistically significant advantage for tafamidis + BSC over placebo + BSC. Responder analysis on the 15% scale range (worsening by ≥ 15 points in the KCCQ-OSS) also showed a clear statistically significant advantage in favour of Tafamidis over BSC.

In the quality of life at month 30, a statistically significant benefit in favour of treatment with tafamidis is derived, which is reflected both in the analysis with a response threshold of ≥ 5 points, and especially in the responder analysis at the 15% scale range (≥ 15 points). Overall, there is a significant advantage in terms of health-related quality of life.

Side effects

Total rates of SAE, discontinuation due to AE

For the endpoints SAEs and discontinuation due to AEs, analyses excluding all SOC Heart disease events are available. For the endpoints SAE and discontinuation due to AE, there were no statistically significant advantages or disadvantages of tafamidis + BSC compared to placebo + BSC in the ATTR-ACT study at month 30.

Dyspnoea (PT, AE)

For the patient-relevant endpoint "dyspnoea", there is an overall statistically significant benefit for PT in the ATTR-ACT study at month 30 in favour of Tafamidis + BSC over placebo + BSC. There is also an effect modification by the feature NYHA classification. While for patients with NYHA Class I + II heart failure there is a statistically significant benefit in favour of tafamidis + BSC over placebo + BSC, for patients with NYHA Class III heart failure there is no difference between tafamidis + BSC and placebo + BSC.

<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 on the basis of the pivotal phase III RCT ATTR-ACT.

In the mortality category, there was a statistically significant benefit in favour of treatment with Tafamidis for overall mortality. In the additionally considered endpoint "cardiovascular mortality", there is also a statistically significant advantage for Tafamidis over BSC.

In the morbidity category, there is a statistically significant advantage for tafamidis for the patient-relevant endpoint walking ability (6MWT), the extent of which cannot be conclusively assessed. For health status (EQ-5D-VAS), a statistically significant, clinically relevant benefit in favour of tafamidis can be derived. Furthermore, an overall advantage for Tafamidis is seen in the morbidity endpoint "hospitalisations", which is, however, relativised by the existing effect modification by the characteristic NYHA classification (class I + II vs class III).
In the quality of life category, there is a clear, statistically significant advantage for Tafamidis over BSC, which is also reflected in particular in the responder analysis for the 15% scale range. Overall, there is a significant advantage in terms of health-related quality of life.

In the endpoint category adverse events, the overall rates show no relevant differences between the treatment groups. For the patient-relevant endpoint "dyspnoea", the ATTR-ACT

study showed an overall statistically significant benefit in favour of Tafamidis over BSC for PT at month 30.

In summary, the statistically significant and clinically relevant advantages of tafamidis over placebo, which are present in three categories, are classified as considerable in their magnitude in the overall view based on the criteria in Section 5 (7) of the AM-NutzenV, taking into account the severity of the disease, the written comments and the oral hearing.

Reliability of data (probability of additional benefit)

With the ATTR-ACT study, a randomised, double-blind Phase III study with a treatment period of 30 months is available for the evaluation of the additional benefit in the indication ATTR-CM.

The ATTR-ACT study population differs from the registration population (diagnosis by scintigraphy according to the product information) with regard to the indication by biopsy. It remains unclear whether patients with ATTR-CM benefit in clinical practice after indication by scintigraphy in the same way as shown in the ATTR-ACT study after biopsy.

The risk of bias is classified as low at study level. At the endpoint level, there is a high potential for bias for the endpoints on hospitalisation and for the results in the endpoint resilience (6MWT), while the bias for the other endpoints is estimated to be low.

For the endpoint "hospitalisations", there are regional differences that may lead to a bias in the number of hospitalisations. It is unclear whether these could be fully offset by randomisation without stratification by country or centre. These regional differences also result in uncertainties regarding the transferability of the results to the German health care context.

Overall, the uncertainties mentioned do not justify a downgrading of the certainty of the results, so that an overall indication of an added benefit is assumed.

2.1.4 Summary of the assessment

The present evaluation is a new benefit assessment of the active ingredient tafamidis due to the exceeding of the €50 million turnover limit.
The present assessment relates to the indication "for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)".

Vyndaqel was authorised under ”exceptional circumstances” as an orphan drug.
The appropriate comparator therapy of Best Supportive Care was determined as follows by the G-BA.

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

In the mortality category, there was a statistically significant benefit in favour of treatment with Tafamidis for overall mortality. In the additionally considered endpoint "cardiovascular mortality", there is also a statistically significant advantage for Tafamidis over BSC.

In the category of morbidity, there is a statistically significant advantage for tafamidis for the patient-relevant endpoint walking ability (6MWT), the extent of which cannot be conclusively assessed. For health status (EQ-5D-VAS), a statistically significant, clinically relevant benefit in favour of tafamidis can be derived. Furthermore, an overall advantage for Tafamidis is seen in the morbidity endpoint "hospitalisations", which is, however, relativised by the existing effect modification by the characteristic NYHA classification (class I + II vs class III).

In the category of quality of life, there is a clear statistically significant advantage for Tafamidis over BSC, which is also reflected in particular in the responder analysis for the 15% scale range. Overall, there is a significant advantage in terms of health-related quality of life.

In the endpoint category adverse events, 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), an indication of considerable additional benefit is inferred based on the benefits of tafamidis over BSC present in three categories.

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

The number of patients is the target population in statutory health insurance (SHI).

The data are based on the patient numbers from the dossier of the pharmaceutical company, as these are based on more recent sources of incidence and prevalence data compared to the initial assessment from 2020[3]. The number of patients in the SHI target population is in a plausible order of magnitude, even if these figures are subject to uncertainties for the individual questions.

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: 1 March 2021):
https://www.ema.europa.eu/documents/product-information/vyndaqel-epar-product-information_de.pdf

Treatment with tafamidis should only be initiated and monitored by doctors experienced in treating patients with amyloidosis cardiomyopathy.

This medicinal product was approved under "exceptional circumstances". This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

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 May 2021).

[3] Resolution of 20 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", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment duration:

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ year
Medicinal product to be assessed				
Tafamidis	Once daily	365	1	365
Best supportive care	varies from patient to patient			
Appropriate comparator therapy				
Best supportive care	varies from patient to patient			

Consumption:

Name of therapy	Dosage/ application	Dosage/ patient/d ays of treatmen t	Usage by strength/day of treatment	Days of treatment/ patient/ Year	Average annual consumption by strength
Medicinal product to be assessed					
Tafamidis	61 mg	61 mg	once 61 mg	365	365 x 61 mg
Best supportive care	varies from patient to patient				
Appropriate comparator therapy					
Best supportive care	varies from patient to patient				

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 strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, 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:

Name of therapy	Packaging 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	30 WKA	€ 27,006.16	€ 1.77	€ 0.00	€ 27,004.39
Best supportive care	varies from patient to patient				
Appropriate comparator therapy					
Best supportive care	varies from patient to patient				
Abbreviations: WKA = soft capsules					

LAUER-TAXE® last revised: 1 May 2021

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 evaluated and the appropriate comparator therapy 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 the standard expenditure in the course of the treatment are not shown.

Because there are no 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 evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 9 April 2019.

On 27 November 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, paragraph 1, number 6 VerfO.

By letter dated 30 November 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products

with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient tafamidis.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2021. The deadline for submitting written statement procedures was 22 March 2021.

The oral hearing was held on 6 April 2021.

By letter of 07 April 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 30 April 2021.

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 May 2021, and the draft resolution was approved.

At its session on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 April 2019	Determination of the appropriate comparator therapy
Working group Section 35a	30 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	6 April 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 April 2021 21 April 2021 5 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	11 May 2021	Concluding consultation of the draft resolution
Plenum	20 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 May 2021

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

Prof. Hecken