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: Reassessment of an orphan drug after exceeding the € 50 million turnover limit (Amyloidosis with polyneuropathy)

of 20 May 2021

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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 trials 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 the therapeutic indication 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 its session on 7 June 2012, the G-BA decided on the benefit assessment of tafamidis in the therapeutic indication “ATTR amyloidosis with polyneuropathy” in accordance with Section 35a 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 25 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

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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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.

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

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult transthyretin amyloidosis patients with stage 1 symptomatic polyneuropathy

Appropriate comparator therapy for tafamidis:

Patisiran

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 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.

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

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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. In addition to tafamidis, the following medicinal products are approved for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy: Patisiran and inotersen.

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

on 3. For the therapeutic indication ATTR amyloidosis with polyneuropathy, the following resolutions on the benefit assessment of medicinal products with new active substances according to Section 35a SGB V are available:
- Patisiran (Resolution of 22 March 2019)
- Inotersen (Resolution of 22 March 2019)
- Tafamidis (Resolution of 7 June 2012)

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

For the present therapeutic indication, the evidence is very limited. No relevant or methodologically adequate systematic reviews or guidelines could be identified.

The two medicinal products patisiran and inotersen are approved for the treatment of ATTR amyloidosis in adult patients with stage 1 symptomatic polyneuropathy. For patisiran and inotersen. the following resolutions on the benefit assessment of medicinal products with new active substances according to Section 35a SGB V are available: For patisiran, considerable additional benefit was identified in the orphan drug assessment (patisiran vs placebo). For inotersen, a non-quantifiable additional benefit was determined in the orphan drug assessment (inotersen vs placebo).

Based on the evidence in the present therapeutic indication, patisiran is determined to be the appropriate comparator therapy for tafamidis for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy.

It is assumed that in both study arms a patient-individual adequate treatment of the respective organ manifestation (such as cardiac insufficiency and/or polyneuropathy) is carried out in accordance with the state of medical knowledge, taking into account the special features of the disease ATTR amyloidosis, and is documented as concomitant treatment.
The therapeutic decision to perform a liver transplant is strongly dependent on a patient-individual risk-benefit assessment and is also only considered for patients who meet

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defined criteria regarding their degree of disease, general condition and age. It is assumed that liver transplantation will not be considered at the time of therapy with tafamidis.

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 transthyretin amyloidosis with stage 1 symptomatic polyneuropathy, the additional benefit of tafamidis compared with the appropriate comparator therapy is not proven.

Justification:

In his dossier for the assessment of the additional benefit of tafamidis, the pharmaceutical company does not present any direct comparative studies regarding the appropriate comparator therapy. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment.

In the absence of directly comparable data in the dossier for the early benefit assessment, the pharmaceutical company examined the possibility of an indirect comparison and came to the conclusion that an indirect comparison of tafamidis with the appropriate comparator therapy was not possible due to the lack of suitable studies.

Thus, overall, no suitable data are available for the assessment of the additional benefit of tafamidis.

2.1.4 Summary of the assessment

The present evaluation is a new benefit assessment of the active substance tafamidis due to the exceeding of the €50 million turnover limit.
The present assessment relates to the therapeutic indication “for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment”.

Vyndaqel was approved under “exceptional circumstances” as an orphan drug.

The G-BA determined patisiran as appropriate comparator therapy. The pharmaceutical company does not present any direct comparative data with the appropriate comparator therapy with the dossier for the assessment of the additional benefit. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment. Thus, no adequate data are available to assess the additional benefit of tafamidis. Overall, for adult patients with transthyretin amyloidosis with stage 1 symptomatic polyneuropathy, the additional benefit of tafamidis compared with the appropriate comparator therapy is not proven.

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

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initial assessment from 2012[2]. Also, these do not challenge the patient counts of the two resolutions from March 2019[3]. The overall number of patients in the SHI target population is subject to uncertainty due to limited information on both the population and all estimated proportions.

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 or polyneuropathy.

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: 01 May 2021).

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.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg) [4].

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				

[2] Resolution on tafamidis Meglumin of 7 June 2012.
[3] Resolution on inotersen and patisiran, respectively, dated 22 March 2019.
[4] Statistisches Bundesamt (Federal Statistic Office), Wiesbaden 2018: http://www.gbe-bund.de/

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Tafamidis	1 x daily	365	1	365
Appropriate comparator therapy				
Patisiran	once every 21 days	17.4	1	17.4

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tafamidis	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Appropriate comparator therapy					
Patisiran	300 µg/kg = 23,1 mg	23,1 mg	3 x 10 mg	17.4	52.2 x 10 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 130a 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. 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:

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Designation of the 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 20 mg	30 WKA	€ 13,365.41	€ 1.77	€ 0.00	€ 13,363.64
Appropriate comparator therapy					
Patisiran	1 IFC	€ 8,845.44	€ 1.77	€ 504.58	€ 8,339.09
Abbreviations: IFK = concentrate for the preparation of an infusion solution; 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.

According to the Onpattro® product information, all patients should receive the following premedication 60 minutes prior to patisiran administration to reduce the risk of infusion-related reactions: Corticosteroid (dexamethasone 10 mg or equivalent, intravenous), paracetamol (500 mg, oral), H1 blocker (diphenhydramine 50 mg or equivalent, intravenous), and H2 blocker (ranitidine 50 mg or equivalent, intravenous). In this context, for premedication medical products that are not available for intravenous use or that are not tolerated, the equivalents can be used orally.

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Designation of the therapy	Packaging size	Costs (pharmacy dispensing price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days / year	Costs/ patient/ year
Appropriate comparator therapy							
Patisiran							
Corticosteroid: Dexamethasone 10 mg, IV.							
Dexamethasone 5 mg[5]	10 ILO	€ 17.16	€ 1.77	€ 0.48	€ 14.91	17.4	€ 51.89
Paracetamol 500 mg, oral							
Paracetamol 500 mg[4,6]	20 TAB	€ 1.50	€ 0.08	€ 0.06	€ 1.36	17.4	€ 1.18
H1 Blockers: Diphenhydramine 50 mg, oral							
Diphenhydramine 50 mg5[.6]	50 TAB	€ 8.75	€ 0.44	€ 0.40	€ 7.91	17.4	€ 2.75
H2 blocker cimetidine: 5 mg/kg IV = 385 mg							
Cimetidine 200 mg[5]	10 AMP	€ 21.55	€ 1.77	€ 0.00	€ 19.78	17.4	€ 68.83
Abbreviations: AMP = ampoules; ILO = solution for injection; TAB = tablets							

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 07 July 2020.

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 December 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

[5]fixed reimbursement rate

[6]Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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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 statements was 23 March 2021.

The oral hearing was held on 06 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	7 July 2020	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
Working group Section 35a	14 April 2021 21 April 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

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