Resolution

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 EUR 50 million turnover limit: amyloidosis in cardiomyopathy)

of 20 May 2021

At its session on 20 May 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive, (AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. **The information on tafamidis in the version of the resolution of 20 August 2020 (BAnz AT DD.MM.YYYY B1) is repealed.**

2. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of tafamidis in accordance with the resolution of 20 May 2021:**

Tafamidis

Resolution of: 20 May 2021
Entry into force on: 20 May 2021
BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 17 February 2020):

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 therapeutic indication according to marketing authorisation

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

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

Appropriate comparator therapy:

Best supportive care

Extent and probability of the additional benefit of tafamidis compared to the best supportive care:

Indication of a considerable additional benefit

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall mortality.
Morbidity	↑	Advantage in hospitalisation, advantage in walking ability, advantage in health status
Health-related quality of life	↑↑	Advantage in quality of life
Side effects	↔	No relevant difference for the benefit assessment.
Explanations:		

[1] Data from the dossier evaluation of the IQWiG (A20-102) and from the annex, unless otherwise indicated.

↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There is no usable data for the benefit assessment.
n.a.: not assessable

ATTR-ACT study (B3461028): Phase III RCT Tafamidis + BSC vs placebo + BSC (relevant study arms; data cut-off at month 30)

Mortality

Study ATTR-ACT **Endpoint**	**Tafamidis + BSC**		**Placebo + BSC**		**Tafamidis + BSC vs. Placebo + BSC**
	N	***Median time to event in months [95% CI]*** **Patients with event n (%)**	**N**	***Median time to event in months [95% CI]*** **Patients with event n (%)**	**HR [95% CI]; p value[a]** **Absolute difference (AD)[2]**
Overall mortality[b]	176	*n.a.* 49 (27.8)	177	*n.a.* 72 (40.7)	0.65 [0.45; 0.93] 0.020 AD: 12.9%
Cardiovascular mortality[b] *(presented additionally)*	176	*n.a.* 40 (22.7)	177	*n.a.* 59 (33.3)	0.64 [0.43; 0.96] 0.029 AD: 10.6%

2 Only in the case of significant results

Morbidity

Study ATTR-ACT Endpoint	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs. Placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[c] Absolute difference (AD)
Hospitalisations (total)					
Total	176	125 (71.0)	177	136 (76.8)	0.92 [0.82; 1.05] 0.247

Study ATTR-ACT Endpoint	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs. Placebo + BSC
	N	Annual rate [95% CI][e]	N	Annual rate [95% CI][e]	Rate-Ratio [95% CI]; p Value[e] Absolute difference (AD)[2]
Hospitalisations (total)					
Total	176	0.96 [0.86; 1.06]	177	1.16 [1.05; 1.29]	0.82 [0.71; 0.95]; 0.009 AD: 0.2
NYHA class I+II	121	0.76 [0.66; 0.87]	114	1.14 [1.01; 1.28]	0.67 [0.56; 0.80] <0.001 AD: 0.38
NYHA class III	55	1.52 [1.29; 1.79]	63	1.21 [1.01; 1.44]	1.26 [0.99; 1.61]; 0.061
					Interaction: < 0.001[f]

Study ATTR-ACT Endpoint	Tafamidis + BSC			Placebo + BSC			Tafamidis + BSC vs. Placebo + BSC
	N	Values at start of study MV (SD)	Change MW (SE) [h]	N	Values at start of study MV (SD)	Change MW (SE)[h]	MD RR [95% CI]; p value[h]
Load capacity by means of 6MWT[i] (to month 30)							
MMRM evaluation	158	344.78 (120.28)	-54.77 (7.46)	152	353.26 (125.98)	-130.54 (9.80)	75.77 [55.99; 95.55] <0.001
Pattern Mixture Model 1							61.31 [36.00; 86.62] <0.001
Pattern Mixture Model 2							63.36 [29.25; 97.47] <0.001
Replacement of missing values by means of MI							70.84 [48.01; 93.66] <0.001
health status							
EQ-5D VAS	160	68.27 (18.36)	-3.43 (1.40)	160	66.48 (17.76)	-12.92 (1.62)	9.49 [6.05; 12.94] <0.001 Hedges' g: 0.60 [0.38; 0.83][j]

Health-related quality of life

Study ATTR-ACT Endpoint Scale	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs. Placebo + BSC
	N	*Median time to event in months [95% CI]* Patients with event n (%)	N	*Median time to event in months [95% CI]* Patients with event n (%)	HR [95% CI]; p value[k] Absolute difference (AD)[2]
KCCQ-OSS					
Improvement by ≥ 5 points	176	*17.81 [11.93; 18.20]* 105 (59.7)	177	*11.99 [11.63; 12.19]* 128 (72.3)	0.62 [0.47; 0.80] <0.001 AD: 5.82 months

Study ATTR-ACT Endpoint Scale	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs. Placebo + BSC
	N	*Median time to event in months [95% CI]* Patients with event n (%)	N	*Median time to event in months [95% CI]* Patients with event n (%)	HR [95% CI]; p value[k] Absolute difference (AD)[2]
Deterioration by ≥ 15 points (corresponds to 15% of the scale span)	176	*30.46 [30.03; n. b]* 64 (36.4)	177	*18.30 [17.71; 23.95]* 95 (53.7)	0,49 [0,35; 0,67]; < 0,001 AD: 12.16 months

Side effects

Study ATTR-ACT Endpoint	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs Placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[c] Absolute difference (AD)[2]
AEs[m] *(presented additionally)*	176	170 (96.6)	177	173 (97.7)	-
SAEs[m]	176	106 (60.2)	177	102 (57.6)	1.05 [0.88; 1.24] 0.683
Discontinuation because of AEsm	176	20 (11.4)	177	28 (15.8)	0.72 [0.42; 1.23] 0.247
Dyspnoea (PT, AE)					
Total	176	29 (16.5)	177	55 (31.1)	0.52 [0,35; 0,77]; 0,001[n] AD: 14.6%
NYHA class I + II	121	17 (14.0)	114	40 (35.1)	0.39 [0.24; 0.65][o]; < 0.001[o] AD: 21.1 %
NYHA class III	55	12 (21.8)	63	15 (23.8)	0.94 [0.49; 1.83][o]; 0.865[o]
					Interaction: 0,037[d]

a. RH, CI and p value: Cox-Proportional-Hazards-Model adjusted for NYHA classification and TTR genotype
b. 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). i.e. the time of study discontinuation is not considered as an event (death) in the analysis (as was done in the authoritative analysis of the pU) or is not censored
c. IQWiG calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to Andrés et al., 1994).
d. IQWiG's own calculation, Cochran's Q-test
e. Mean rates with CI (per treatment group) and rate ratio with CI and p-value (group comparison): Poisson regression with the variables treatment, TTR genotype, NYHA classification and the interaction terms between treatment and TTR genotype as well as between treatment and NYHA classification; according to the company adjusted for the observation period with treatment. It remains unclear whether this is the observation or treatment period.
f. Poisson regression with corresponding interaction term
g. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at baseline (possibly at other times) can be based on other patient numbers.
H. MW and SE (change to week 30 per treatment group) and MD, CI and p-value (group comparison): MMRM evaluation with the variables treatment, visit, value at baseline, TTR genotype and the interaction term between treatment and visit
i. Higher (increasing) values mean an improvement in symptomatology/health-related quality of life; positive effects ([tafamidis + BSC] minus [placebo + BSC]) mean an advantage for tafamidis + BSC.
j. IQWiG's own calculation based on the MD and CI of the MMRM
k. HR, 95% CI and p value: Cox-Proportional-Hazards-Model adjusted for value at baseline and TTR genotype
l. Symptom burden and symptom frequency
m. without SOC Heart disease events
n. RR, CI and p-value: generalised linear model adjusted for TTR genotype and NYHA classification
o. Generalised linear model adjusted for TTR genotype

BSC: Best supportive care; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; HR: Hazard Ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; KI: Confidence interval; MD: Mean difference; MMRM: mixed model with repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: Number of patients evaluated; n.a.: not achieved; NYHA: New York Heart Association; OSS: Overall Summary Score; PT preferred term; PT: preferred term; RCT: randomised controlled study; RR: relative risk; SD: Standard deviation; SE: standard error; SMD: Standardised mean difference; SOC: System organ class; SAE: serious adverse event; TTR: Transthyretin; AE: adverse event; VAS: visual analogue scale; 6MWT: 6-minute walking test (6MWT)

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 1.760 to 1.810 patients

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.

4. Treatment costs

Annual treatment costs:

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

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Tafamidis	€ 328,553.41
Best supportive care	varies from patient to patient
Appropriate comparator therapy:	
Best supportive care	varies from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 1 May 2021).

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 20 May 2021.

The justification for this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 20 May 2021

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

Prof. Hecken