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

At its session on 20 August 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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:

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 7 June 2012:

Tafamidis

Resolution of: 20 August 2020
Entry into force on: 20 August 2020
Federal Gazette, 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).

1. Extent of the additional benefit and the significance of the proof

Tafamidis is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adult patients with wild type or hereditary transthyretin amyloidosis with cardiomyopathy

Extent of the additional benefit and the significance of the proof for tafamidis:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

Adult patients with wild type or hereditary transthyretin amyloidosis with cardiomyopathy

ATTR-ACT study (B3461028): Phase-III RCT tafamidis vs. placebo (relevant study arms; data cut-off at Month 30)

[1] Data from the dossier assessment by the G-BA (published on 2 June 2020) as well as from the amendment unless indicated otherwise.

Mortality (ITT population)

Endpoint ATTR-ACT study	Tafamidis		Placebo		Tafamidis vs placebo
	N	Median survival[a] in months [95% CI] *Patients with event n (%)*	N	Median survival[a] in months [95% CI] *Patients with event n (%)*	HR [95% CI][b]; p value
Overall mortality[c]	176	n.a. [n.a.; n.a.] *49 (27.8)*	177	n.a. [n.a.; n.a.] *72 (40.7)*	0.65 [0.45; 0.93] 0.0199
Cardiovascular mortality[c,d] *(presented additionally)*	176	no data available *40 (22.7)*	177	no data available *59 (33.3)*	0.64 [0.43; 0.96] 0.0290

Morbidity (ITT population)

Endpoint ATTR-ACT study	Tafamidis		Placebo		Tafamidis vs placebo
	N or n/N (%)[e]	Annual rate[f] [95% CI]	N or n/N (%)[e]	Annual rate[f] [95% CI]	Rate ratio[f] [95% CI]; exact p value
Hospitalisations					
Frequency of all hospitalisations					
Total	125 (71.0)	0.96 [0.86; 1.06]	136 (76.8)	1.16 [1.05; 1.29]	0.82 [0.71; 0.95]; 0.0089
NYHA class I + II	80/121 (66.1)	0.76 [0.66; 0.87]	86/114 (75.4)	1.14 [1.01; 1.28]	0.67 [0.56; 0.80]; p < 0.001
NYHA class III	45/55 (81.8)	1.52 [1.29; 1.79]	50/63 (79.4)	1.21 [1.01; 1.44]	1.26 [0.99; 1.61]; p = 0.0613

Endpoint Study ATTR-ACT	Tafamidis			Placebo			Tafamidis vs placebo
	N (%)[g]	MV Walking distance in metres (SD)	*n (%)[h]* *MV (SD)* n (%)[i] LS-MV (SE)[j,k]	N (%)[g]	MV Walking distance in metres (SD)	*n (%)[h]* *MV (SD)* n (%)[i] LS-MV (SE)[j,k]	Difference of the LS mean LS-MD [95% CI][j,k] p value
Walking ability (6MWT)							
Baseline	176 (100)	344.78 (120.28)	-	177 (100)	353.26 (125.98)	-	
Month 18	128 (85)	no data available		111 (76)	no data available		-
Month 30 *(presented additionally)*	101 (57)	364.73 (126.08)		70 (40)	333.76 (117.45)		
Change in walking distance in meters at Month 18 compared with baseline	-		*28 (85)* *no data available* 158 (90) −39.02 (6.74)	-		*111 (76)* *no data available* 152 (86) −84.07 (8.49)	45.04 [27.30; 62.79] < 0.0001 Hedges' g: 0.54 [0.28; 0.80]
Change in walking distance in meters at Month 30 compared with baseline*(presented additionally)*	-		*101 (57)* *−31.17* *(85.33)* 158 (90) −54.77 (7.46)	-		*70 (40)* *−89.67* *(105.16)* 152 (86) −130.54 (9.80)	75.77 [55.99; 95.55] < 0.0001 Hedges' g: 0.97 [0.65; 1.29]

Endpoint Study ATTR-ACT	Tafamidis			Placebo			Tafamidis vs placebo
	N (%)[g]	MV (SD)	*n (%)[h]* *MV (SD)* n (%)[i] LS-MV (SE)[j,k]	N (%)[g]	MV (SD)	*n (%)[h]* *MV (SD)* n (%)[i] LS-MV (SE)[j,k]	Difference of the LS mean LS-MD [95% CI][j,k] p value
Health status (EQ-5D-VAS)							
Baseline	173 (98)	68.27 (18.36)	-	177 (100)	66.48 (17.76)	-	

Endpoint Study ATTR-ACT	Tafamidis			Placebo			Tafamidis vs placebo
	N (%)[g]	MV (SD)	*n (%)[h]* *MV (SD)* n (%)[i] LS-MV (SE)[j,k]	N (%)[g]	MV (SD)	*n (%)[h]* *MV (SD)* n (%)[i] LS-MV (SE)[j,k]	Difference of the LS mean LS-MD [95% CI][j,k] p value
Month 30	109 (62)	68.91 (18.22)		84 (47)	58.04 (21.43)		9.49 [6.05; 12.94] < 0.0001; Hedges' g: 0.65 [0.35; 0.94]
Change at Month 30 compared with baseline	-		*106 (60)* *−2.21* *(16.51)* 160 (91) −3.43 (1.40)	-		*84 (47)* *−9.96* *(20.73)* 160 (90) −12.92 (1.62)	

Health-related quality of life (ITT population)

Endpoint ATTR-ACT study	Tafamidis		Placebo		Tafamidis vs placebo
	N	Median time in months[a] [95% CI] *Patients with event n (%)*	N	Median time in months[a] [95% CI] *Patients with event n (%)*	HR [95% CI][l]; p value
KCCQ-OSS					
First improvement in KCCQ-OSS by ≥ 5 points compared with baseline	176	20.11 [12.35; n.a.] *76 (43.2)*	177	n.a. [24.05; n.a.] *61 (34.5)*	1.27 [0.90, 1.77] 0.1716
First deterioration in KCCQ-OSS by ≥ 5 points compared with baseline	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] 0.0003
"permanent" deterioration in KCCQ-OSS by ≥ 5 points (on three consecutive rounds)	176	n.a. [n.a.; n.a.] *35 (19.9)*		n.a. [n.a.; n.a.] *54 (30.5)*	0.50 [0.33, 0.77] 0.0016

Endpoint Study ATTR-ACT	Tafamidis			Placebo			Tafamidis vs placebo
	N (%)[h]	MV (SD)	*n (%)[i]* *MV (SD)* n (%)[j] LS-MV (SE)[k,l]	N (%)[h]	MV (SD)	*n (%)[i]* *MV (SD)* n (%)[j] LS-MV (SE)[k,l]	Difference of the LS mean LS-MD [95% CI][k,l] p value
KCCQ-OSS							
Baseline	176 (100)	67.12 (21.29)		177 (100)	65.90 (21.74)		
Month 30	110 (63)	68.76 (21.42)		84 (47)	53.83 (24.42)		
Change at Month 30 compared with baseline			*110 (63)* *−3.91* *(19.29)* 163 (93) −7.34 (1.50)			*84 (47)* *−14.64* *(21.41)* 160 (90) −20.82 (1.98)	13.48 [9.16; 17.80] < 0.0001 Hedges' g: 0.80 [0.50; 1.09]

Side effects (safety population)

Study ATTR-ACT Endpoint	Tafamidis		Placebo		Tafamidis vs placebo
	N	Median time in months[a] [95% CI] *Patients with event n (%)*	N	Median time in months[a] [95% CI] *Patients with event n (%)*	HR [95% CI][b]; p value
AE	176	0.92 [0.62; 1.15] *173 (98.3)*	177	0.95 [0.69; 1.22] *175 (98.9)*	-
Severe AE	176	20.04 [14.72; 24.54] *110 (62.5)*	177	19.68 [14.32; 23.39] *114 (64.4)*	0.94 [0.72; 1.22] 0.6378
SAE	176	12.39 [8.74; 16.49] *133 (75.6)*	177	10.64 [8.8; 15.38] *140 (79.1)*	0.92 [0.72; 1.17] 0.4901
Therapy discontinuation because of AE	176	n.a. [n.a.; n.a.] *40 (22.7)*	177	n.a. [n.a.; n.a.] *51 (28.8)*	0.75 [0.49; 1.13] 0.1665

Study ATTR-ACT **MedDRA System Organ Class** Preferred Term	**Tafamidis**		**Placebo**		**Tafamidis vs placebo**
	Persons with event N = 176 *n (%)*	Median in months[a] [95% CI]	Persons with event N = 177 *n (%)*	Median in months [95% CI][a]	HR [95% CI] p value[b]
AE by SOC and PT with incidence ≥ 10% in one of the two treatment groups and a difference ≥ 10% between the treatment groups (safety population)					
Respiratory, thoracic and mediastinal disorders	**76 (43.2)**	**n.a. [18.4; n.a.]**	**111 (62.7)**	**15.01 [11.7; 19.55]**	**0.57 [0.42; 0.76] 0.0001**
Dyspnoea	29 (16.5)	n.a. [n.a.; n.a.]	55 (31.1)	n.a. [31.01; n.a.]	0.46 [0.29; 0.73] 0.0009
Pleural effusion	14 (8.0)	n.a. [n.a.; n.a.]	32 (18.1)	n.a. [n.a.; n.a.]	0.39 [0.21; 0.73] 0.0031
Renal and urinary disorders	**55 (31.3)**	**n.a. [n.a.; n.a.]**	**74 (41.8)**	**27.17 [22.51; n.a.]**	**0.65 [0.45; 0.92] 0.0148**
Metabolism and nutrition disorders	**73 (41.5)**	**n.a. [27.24; n.a.]**	**110 (62.1)**	**19.29 [15.15; 22.44]**	**0.53 [0.39; 0.71] < 0.0001**
Severe adverse events by SOC and PT with incidence ≥ 5% in one of the two treatment groups and a difference ≥ 5% between the treatment groups					
Cardiac disorders	**61 (34.7)**	**n.a. [n.a.; n.a.]**	**75 (42.4)**	**30.06 [23.92; n.a.]**	**0.74 [0.53; 1.04] 0.0854**
Metabolism and nutrition disorders	**9 (5.1)**	**n.a. [n.a.; n.a.]**	**18 (10.2)**	**n.a. [n.a.; n.a.]**	**0.49 [0.22; 1.08] 0.0781**
Injury, poisoning and procedural complications	**19 (10.8)**	**n.a. [n.a.; n.a.]**	**9 (5.1)**	**n.a. [n.a.; n.a.]**	**2.03 [0.92; 4.50] 0.0807**
SAE by SOC and PT with incidence ≥ 5% in one of the two treatment groups and a difference ≥ 5% between the treatment groups					
Cardiac disorders	**86 (48.9)**	**28.42 [23.33; n.a.]**	**97 (54.8)**	**21.88 [18.56; 26.22]**	**0.82 [0.61; 1.10] 0.1869**
Congestive heart failure	20 (11.4)	n.a. [n.a.; n.a.]	32 (18.1)	n.a. [n.a.; n.a.]	0.59 [0.34; 1.04] 0.0690
Metabolism and nutrition disorders	**14 (8.0)**	**n.a. [n.a.; n.a.]**	**24 (13.6)**	**n.a. [n.a.; n.a.]**	**0.57 [0.29; 1.10] 0.0942**
Injury, poisoning and procedural complications	**24 (13.6)**	**n.a. [n.a.; n.a.]**	**14 (7.9)**	**n.a. [n.a.; n.a.]**	**1.72 [0.89; 3.33] 0.1097**

a: Kaplan-Meier estimator.
b: Cox proportional hazard model with TTR genotype and NYHA classification at baseline (Class I + II vs Class III) as factors.
c: Persons with heart transplant or combined heart/liver transplant or mechanical circulatory support were further observed after their surgeries.
d: Consisting of cardiovascular deaths and unspecified deaths.
e: Number of persons with at least one hospitalisation.
f: Poisson regression adjusted for treatment duration with treatment, stratification variables, interaction treatment*TTR genotype, and interaction treatment*NYHA classification at baseline (Class I + II vs Class III) as factors.
g: Number of persons with return at the respective time.
h: Number of people with results in 6MWT at baseline and Month 30.
i: Number of people with results in 6MWT at baseline and a further survey post-baseline.
j: All persons whose TTR genotyping was available and with baseline survey and at least one post-baseline survey were included in the analysis.
k: ANCOVA (MMRM) of an unstructured covariance matrix; baseline value as covariance and treatment, rounds, TTR genotype, and the interaction rounds*treatment as fixed effects, and centre and person-in-centre as random effects
l: Cox proportional hazard model with TTR genotype, treatment, and baseline value as factors

Abbreviations: 6MWT: 6 minute walk test; ANCOVA Analysis of covariance; EQ-5D-VAS: Visual analogue scale of the EuroQol 5-dimensional questionnaire; HR: Hazard Ratio; ITT: Intention-to-Treat; KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire – Overall Summary Score; CI: confidence interval; LS-MV: least squares mean value; LS-MD: least squares mean difference; MMRM: mixed model with repeated measurements; MV: mean value; N: number of patients with (at least one) event; n.a.: not applicable; NYHA New York Heart Association; SD: standard deviation; SE: standard error; SUE: serious adverse event(s), TTR: transthyretin. AE: adverse event(s); vs = versus

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 differences relevant for the benefit assessment.

Explanations:
↑: 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 are no usable data for the benefit assessment.
n.a.: not assessable

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

Adult patients with wild type or hereditary transthyretin amyloidosis with cardiomyopathy

approx. 1,630–1,730 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: 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.

4. Treatment costs

Annual treatment costs:

Adult patients with wild type or hereditary transthyretin amyloidosis with cardiomyopathy

Designation of the therapy	Annual treatment costs/patient
Tafamidis	€ 320,269.98

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 August 2020

Costs for additionally required SHI services: not applicable

I. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 20 August 2020.

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

Berlin, 20 August 2020

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

Prof. Hecken