Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Vadadustat (symptomatic anaemia in dialysis-dependent chronic kidney disease)

of 22 November 2024

At its session on 22 November 2024, 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Vadadustat as follows:

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Vadadustat

Resolution of: 22 November 2024
Entry into force on: 22 November 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 24 April 2024):

Vafseo is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis.

Therapeutic indication of the resolution (resolution of 22 November 2024):

See therapeutic indication according to marketing authorisation.

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

Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis

Appropriate comparator therapy:

Darbepoetin alfa or epoetin alfa or epoetin beta or epoetin theta or epoetin zeta or methoxy polyethylene glycol epoetin beta

Extent and probability of the additional benefit of vadadustat compared to darbepoetin alfa:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis

[1] Data from the dossier assessment of the IQWiG (A24-67) and from the addendum (A24-106), unless otherwise indicated.

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Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant differences for the benefit assessment. Advantage for the SAE endpoint and in detail for specific AEs; disadvantage for the endpoint of therapy discontinuation due to AEs.

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
∅: No data available.
n.a.: not assessable

CI-0016 and CI-0017 studies: open-label RCTs; vadadustat vs darbepoetin alfa

Mortality

Endpoint Study	Vadadustat		Darbepoetin alfa		Vadadustat vs darbepoetin alfa
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p value[a]
Overall mortality					
CI-0016	179	n.r. 15 (8.4)	186	n.r. 20 (10.8)	0.78 [0.39; 1.56]; 0.512
CI-0017	1768	n.r. 276 (15.6)	1769	n.r. 290 (16.4)	0.96 [0.82; 1.14]; 0.581
Total					0.95 [0.81; 1.12]; 0.488[b]

Morbidity

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Endpoint Study	Vadadustat		Darbepoetin alfa		Vadadustat vs darbepoetin alfa
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[c]
Transfusion independence (presented additionally)					
CI-0016	179	n.d.	186	n.d.	0.97 [0.90; 1.05][d]; n.d.
CI-0017	1768	n.d.	1769	n.d.	0.98 [0.96; 1.01][d]; n.d.
Total	1947	1621 (83.3)	1955	1659 (84.9)	0.98 [0.96; 1.01]; 0.190[f]

Health-related quality of life

Not assessed

Side effects

Endpoint Study	Vadadustat		Darbepoetin alfa		Vadadustat vs darbepoetin alfa
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[c]
AEs (presented additionally)					
CI-0016	179	150 (83.8)	186	159 (85.5)	-
CI-0017	1768	1562 (88.3)	1769	1580 (89.3)	-
SAEs					
CI-0016	179	89 (49.7)	186	105 (56.5)	0.87 [0.71; 1.05]; 0.151[e]
CI-0017	1768	973 (55.0)	1769	1032 (58.3)	0.94 [0.89; 0.99]; 0.029[e]
Total					0.93 [0.89; 0.99]; 0.013[f]
Therapy discontinuation due to AEs					
CI-0016	179	5 (2.8)	186	2 (1.1)	2.60 [0.50; 13.60]; 0.242[e]

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CI-0017	1768	91 (5.2)	1769	20 (1.1)	4.50 [2.79; 7.26]; < 0.001[e]
Total					4.31 [2.72; 6.83]; < 0.001[f]
MACE[g]					
CI-0016	179	16 (8.9)	186	14 (7.5)	1.19 [0.60; 2.36]; 0.712
CI-0017	1768	209 (11.8)	1769	228 (12.9)	0.92 [0.77; 1.09]; 0.530
Total					0.93 [0.79; 1.11]; 0.421[h]
Cardiovascular mortality[i]					
CI-0016	179	9 (5.0)	186	10 (5.4)	0.94 [0.39; 2.25]; 0.897
CI-0017	1768	141 (8.0)	1769	150 (8.5)	0.94 [0.75; 1.17]; 0.683
Total					0.94 [0.76; 1.16]; 0.572[h]
Non-fatal myocardial infarction[i]					
CI-0016	179	5 (2.8)	186	3 (1.6)	1.73 [0.42; 7.14]; 0.533
CI-0017	1768	77 (4.4)	1769	85 (4.8)	0.91 [0.67; 1.23]; 0.533
Total					0.93 [0.70; 1.25]; 0.649[h]
Non-fatal stroke[i]					
CI-0016	179	4 (2.2)	186	3 (1.6)	1.39 [0.31; 6.10]; 0.720
CI-0017	1768	28 (1.6)	1769	40 (2.3)	0.70 [0.43; 1.13]; 0.147
Total					0.75 [0.48; 1.18]; 0.208[h]
Hospitalisation due to heart failure					
CI-0016	179	11 (6.1)	186		1.63 [0.65; 4.12]; 0.310
7 (3.8)	1768	73 (4.1)	1769		0.89 [0.65; 1.21]; 0.533

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82 (4.6)					0.95 [0.71; 1.27]; 0.720[h]
Thromboembolic events[j]					
CI-0016	179	7 (3.9)	186	13 (7.0)	0.56 [0.23; 1.37]; 0.247
CI-0017	1768	162 (9.2)	1769	135 (7.6)	1.20 [0.96; 1.49]; 0.103
Total					1.15 [0.93; 1.42]; 0.209[h]
Arterial thrombosis					
CI-0016	179	0 (0)	186	0 (0)	–
CI-0017	1768	7 (0.4)	1769	4 (0.2)	1.75 [0.51; 5.97]; 0.530
Deep vein thrombosis					
CI-0016	179	0 (0)	186	3 (1.6)	0.15 [0.01; 2.85]; 0.097
CI-0017	1768	15 (0.8)	1769	17 (1.0)	0.88 [0.44; 1.76]; 0.794
Total					0.76 [0.39; 1.47]; 0.412[h]
Pulmonary embolism					
CI-0016	179	0 (0)	186	1 (0.5)	0.35 [0.01; 8.45]; 0.515
CI-0017	1768	5 (0.3)	1769	8 (0.5)	0.63 [0.20; 1.91]; 0.530
Total					0.58 [0.20; 1.66]; 0.312[f]
Vascular access thrombosis					
CI-0016	179	7 (3.9)	186	9 (4.8)	0.81 [0.31; 2.12]; 0.712
CI-0017	1768	139 (7.9)	1769	111 (6.3)	1.25 [0.98; 1.59]; 0.071
Total					1.22 [0.97; 1.54]; 0.094[f]
Liver toxicity (SMQ, SAE)[k]					
CI-0016	179	5 (2.8)	186	6 (3.2)	0.94 [0.27; 3.30]; 0.926[e]

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CI-0017	1768	45 (2.5)	1769	46 (2.6)	0.98 [0.65; 1.46]; 0.906[e]
Total					0.97 [0.66; 1.43]; 0.888[f]
Cardiac disorders (SOC, SAE)					
CI-0016	179	23 (12.8)	186	25 (13.4)	0.96 [0.56; 1.62]; 0.878[l]
CI-0017	1768	296 (16.7)	1769	353 (20.0)	0.84 [0.73; 0.96]; 0.015[l]
Total					0.85 [0.74; 0.97]; 0.015[f]
Benign, malignant and unspecified neoplasms (SOC, SAE)					
CI-0016	179	2 (1.1)	186	4 (2.2)	0.52 [0.10; 2.80]; 0.533
CI-0017	1768	38 (2.1)	1769	58 (3.3)	0.66 [0.44; 0.98]; 0.049[l]
Total					0.65 [0.44; 0.96]; 0.030[f]
Urinary tract infection (PT, SAE)					
CI-0016	179	2 (1.1)	186	1 (0.5)	2.08 [0.19; 22.72]; 0.600
CI-0017	1768	15 (0.8)	1769	32 (1.8)	0.47 [0.25; 0.86]; 0.018[l]
Total					0.51 [0.28; 0.93]; 0.027[f]
Changed state of mind (PT, SAE)					
CI-0016	179	0 (0)	186	2 (1.1)	0.21 [0.01; 4.30]; 0.225
CI-0017	1768	11 (0.6)	1769	23 (1.3)	0.48 [0.23; 0.98]; 0.056[l]
Total					0.46 [0.23; 0.92]; 0.028[f]

a. HR and 95% CI from Cox regression model, p value from log-rank test. The analyses are each stratified by geographical region (USA/ EU/ rest of the world), NYHA heart failure class (0 or I / II or III), Hb value at baseline, sex (male/ female), age (> 65/ ≤ 65 years), descent (white / other), history of cardiovascular disease (yes/ no) and presence of diabetes mellitus (yes/ no)

b. IPD meta-analysis: HR and 95% CI from Cox regression model, p value from log-rank test. Stratification factors: as for the individual studies, additionally stratified by study effect and CI: IQWiG calculation

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c. Unless otherwise stated: IQWiG calculation of effect, CI (asymptotic) and p value (unconditional exact test, CSZ method). In the case of 0 events in one study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI.
d. Effect calculation via four-field table, CI via normal distribution assumption
e. RR: stratified by geographical region (USA/ EU/ rest of the world), NYHA heart failure class (0 or I/ II or III), Hb value at baseline (< 9.5/ ≥ 9.5 g/dl in CI 0016 study or < 10.0/ ≥ 10.0 g/dl in CI-0017 study), CI: normal distribution approximation, p value: Cochran-Mantel-Haenszel test
f. Meta-analysis with fixed effects (inverse variance), CI and p value via normal distribution approximation
g. Composite cardiovascular endpoint consisting of the components "cardiovascular death", "non-fatal myocardial infarction" and "non-fatal stroke"; after review by the Endpoint Adjudication Committee
h. IQWiG calculation: Meta-analysis with fixed effect (Mantel and Haenszel method)
i. The 1st event in this endpoint was taken into account, regardless of whether it is also the 1st event in the composite endpoint MACE.
j. Consisting of the components: arterial thrombosis, deep vein thrombosis, pulmonary embolism and vascular access thrombosis, after review by the Endpoint Adjudication Committee
k. Operationalised as comprehensive SMQ broad
l. RR: unstratified, CI: normal distribution approximation, p value: Fisher test

Abbreviations used:
EU: European Union; Hb: haemoglobin; HR: hazard ratio; CI: confidence interval; MACE: Major Adverse Cardiovascular Event; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients evaluated; n: number of patients with (at least 1) event; NYHA: New York Heart Association; n.r.: not reached; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SMQ: standardised MedDRA query; SOC: system organ class; SAE: serious adverse event; AE: adverse event

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

Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis

Approx. 60,800 – 71,400 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 Vafseo (active ingredient: vadadustat) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 6 September 2024):

https://www.ema.europa.eu/en/documents/product-information/vafseo-epar-product-information_en.pdf

Treatment with vadadustat should only be initiated and monitored by doctors experienced in anaemia treatment.

Treatment should not be continued beyond 24 weeks if no clinically significant increase in haemoglobin levels is achieved.

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4. Treatment costs

Annual treatment costs:

Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Vadadustat	€ 2,995.87 - € 11,876.28
Appropriate comparator therapy:	
Darbepoetin alfa	Not calculable
Epoetin alfa	€ 1,529.14 - € 8,918.48
Epoetin beta	€ 2,469.80 - € 24,961.11
Epoetin theta	€ 2,469.80 - € 24,961.11
Epoetin zeta	€ 1,529.14 - € 8,918.48
Methoxy PEG epoetin beta	Not calculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2024)

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

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II. **The resolution will enter into force on the day of its publication on the website of the G-BA on 22 November 2024.**

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

Berlin, 22 November 2024

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

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