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)
Fezolinetant (vasomotor symptoms (VMS), associated with menopause)

of 1 August 2024

At its session on 1 August 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 Fezolinetant as follows:

Fezolinetant

Resolution of: 1 August 2024
Entry into force on: 1 August 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 7 December 2023):

Veoza is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

Therapeutic indication of the resolution (resolution of 1 August 2024):

See therapeutic indication according to marketing authorisation.

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

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

Appropriate comparator therapy:

- Therapy according to doctor's instructions with a choice of systemic hormone replacement therapy (oestrogen/progestogen combination in women with an intact uterus or oestrogen only in women without a uterus)

Extent and probability of the additional benefit of fezolinetant compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

Appropriate comparator therapy:

- Monitoring wait-and-see approach

Extent and probability of the additional benefit of fezolinetant compared to a monitoring wait-and-see approach:

Hint for a minor additional benefit.

Study results according to endpoints:[1]

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

No data available.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.
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		

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantages in the reduction of moderate and severe vasomotor symptoms and in sleep disorders.
Health-related quality of life	↑	Advantages in health-related quality of life (MENQOL).
Side effects	↔	No relevant differences for the benefit assessment.
Explanations:		

[1] Data from the dossier assessment of the IQWiG (A24-15) and from the addendum (A24-69), 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 ∅: No data available. n.a.: not assessable

DAYLIGHT study: Fezolinetant vs monitoring wait-and-see approach (placebo)

Relevant sub-population: Patients who are ineligible for hormone replacement therapy, operationalised by the presence of at least 1 of the criteria contraindication, discontinuation of hormone replacement therapy or decision against hormone replacement therapy.

Mortality

Endpoint	**Fezolinetant**		**Placebo**		**Fezolinetant vs placebo**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Overall mortality	195	0 (0)	186	0 (0)	-

Morbidity

Endpoint	**Fezolinetant**		**Placebo**		**Fezolinetant vs placebo**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value Absolute difference (AD)[a]
Moderate/ severe VMS (reduction by 100%)[b]	195	47 (24.1)	186	19 (10.2)	2.34 [1.43; 3.83]; < 0.001[c] AD: 28 (13.9)
Mild/ moderate/ severe VMS (reduction by 100 %)[d] (presented additionally)	*195*	*32 (16.4)*	*186*	*9 (4.8)*	*3.38 [1.66; 6.88]; < 0.001[c] AD: 23 (11.6)*
Sleep disorders (PROMIS SD SF 8b, improvement ≥ 7.14 points)[e]	195	99 (50.8)	185	52 (28.1)	1.74 [1.33; 2.26]; < 0.001[c] AD: 47 (22.7)

Endpoint	Fezolinetant		Placebo		Fezolinetant vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value Absolute difference (AD)[a]
Sexual functioning (FSFI, improvement ≥ 5.1 points)[f]	195	36 (18.5)	184	33 (17.9)	1.06 [0.69; 1.61]; 0.803[c]
General symptoms of depression and anxiety disorders (PHQ-4, (improvement ≥ 1.8 points)[g]	195	71 (36.4)	184	50 (27.2)	1.23 [0.94; 1.62]; 0.137[c]
Health status (EQ-5D VAS, improvement ≥ 15 points)[h]	195	30 (15.4)	184	26 (14.1)	1.09 [0.67; 1.77]; 0.731[c]

Health-related quality of life

Endpoint	Fezolinetant		Placebo		Fezolinetant vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value Absolute difference (AD)[a]
MENQOL (improvement ≥ 1.05 points)[i]					
Vasomotor	195	136 (69.7)	184	89 (48.4)	1.45 [1.23; 1.73]; < 0.001[c] AD: 47 (21.3)
Psychosocial	195	94 (48.2)	184	62 (33.7)	1.35 [1.08; 1.69]; 0.009[c] AD: 32 (14.5)
Physical	195	87 (44.6)	184	54 (29.3)	1.47 [1.14; 1.89]; 0.003[c] AD: 33 (15.3)
Sexual	195	72 (36.9)	184	47 (25.5)	1.33 [1.02; 1.75]; 0.036[c] AD: 25 (11.4)

Side effects

Endpoint	Fezolinetant		Placebo		Fezolinetant vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value Absolute difference (AD)[a]
Total adverse events (presented additionally)[j]					
	195	126 (64.6)	186	111 (59.7)	-
Serious adverse events (SAEs)[j]					
	195	7 (3.6)	186	6 (3.2)	1.11 [0.38; 3.25]; > 0.999[l]
Therapy discontinuation due to adverse events[j]					
	195	11 (5.6)	186	13 (7.0)	0.81 [0.37; 1.76]; 0.675[l]
Specific adverse events					
Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC, SAEs)	195	0 (0)	186	0 (0)	-
Liver-related investigations, clinical signs and symptoms (SMQ, SAEs)[k]	195	2 (1.0)	186	0 (0)	4.77 [0.23; 98.71]; 0.499[l]

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation

b. Percentage of patients with a 100% reduction in the average daily frequency of moderate and severe hot flushes compared to the start of the study.

c. RR, 95% CI and p value based on log-binomial regression with treatment group and smoking status (current vs former/never) as factors and the baseline value as covariate. Missing values were replaced using non-responder imputation.

d. Percentage of patients with a 100% reduction in the average daily frequency of mild, moderate and severe hot flushes compared to the start of the study.

e. A decrease in the PROMIS SD SF 8b score by ≥ 15% (≥ 7.14 points) compared to the start of the study is considered a clinically relevant improvement (scale range based on transformed T-score values 28.9 to 76.5).

f. A decrease in the FSFI score by ≥ 15% (≥ 5.01 points) compared to the start of the study is considered a clinically relevant improvement (scale range 2 to 36). The following domains were surveyed: Desire, arousal, lubrication, orgasm, general satisfaction, pain. There are no statistically significant differences.

g. A decrease in PHQ-4 score by ≥ 15% (≥ 1.8 points) compared to the start of the study is considered a clinically relevant improvement (scale range 0 to 12). The following subscales were surveyed: Anxiety, depression. There are no statistically significant differences.

h. An increase in EQ-5D VAS score by ≥ 15% (≥ 15 points) compared to the start of the study is considered a clinically relevant improvement (scale range 0 to 100).

i. A decrease in the MENQOL score in the 4 individual domains: vasomotor, psychosocial, physical and sexual by ≥ 15% each (≥ 1.05 points) compared to the start of the study is considered a clinically relevant improvement (scale range 1

to 8).
j. Contains events of the underlying disease
k. Predefined as AESI in the study
l. RR based on unstratified Mantel-Haenszel test, 95% CI based on Wald. p value based on Fisher exact test

Abbreviations used:
AD = absolute difference: FSFI: Female Sexual Function Index; CI: confidence interval; MENQOL: Menopause-specific Quality of Life questionnaire; n: number of patients with (at least 1) event; N: number of patients evaluated; PGI-C: Patient Global Impression of Change, PHQ: Patient Health Questionnaire; PROMIS: Patient-reported Outcomes Measurement Information System; RR: relative risk; SD: sleep disturbance; SF 8b: Short Form 8b; SMQ: standardised MedDRA query; SOC: system organ class; SAE: serious adverse event; AE: adverse event; AESI: adverse events of special interest; VAS: visual analogue scale; VMS: vasomotor symptoms; vs = versus

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

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

Approx. 517,930 to 603,180 patients

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

Approx. 2,071,720 to 2,412,720 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 Veoza (active ingredient: fezolinetant) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 16 April 2024):

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

The benefit of long-term treatment must be reviewed regularly since the duration of VMS can vary from one subject to another. Women undergoing oncological treatment (e.g. chemotherapy, radiotherapy, anti-hormone therapy) for breast cancer or other oestrogen-related malignancies were not enrolled in the clinical studies. Therefore, fezolinetant is not recommended for use in this population as safety and efficacy are unknown.

4. Treatment costs

Annual treatment costs:

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Fezolinetant	€ 905.86
Appropriate comparator therapy:	
Therapy according to doctor's instructions with a choice of systemic hormone replacement therapy (oestrogen/progestogen combination in women with an intact uterus or oestrogen only in women without a uterus)	
Oestrogen/progestogen combination	
Estradiol + drospirenone[2]	€ 144.91
Oestrogen only	
Estradiol[2]	€ 69.44 - € 72.93

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2024)

Costs for additionally required SHI services: not applicable

2 Fixed reimbursement rate

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Fezolinetant	€ 905.86
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Not calculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 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:

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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.

II. **The resolution will enter into force on the day of its publication on the website of the G-BA on 1 August 2024.**

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

Berlin, 1 August 2024

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

Prof. Hecken