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 Eptinezumab (prophylaxis of migraine)

of 16 February 2023

At its session on 16 February 2023, 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 Eptinezumab as follows:

Eptinezumab

Resolution of: 16 February 2023
Entry into force on: 16 February 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 24 January 2022):

VYEPTI is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

Therapeutic indication of the resolution (resolution of 16 February 2023):

See [new] therapeutic indication according to marketing authorisation.

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

a) Adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine

Appropriate comparator therapy for eptinezumab for prophylaxis of migraine:

- Metoprolol or propranolol or flunarizine or topiramate or amitriptyline or clostridium botulinum toxin type A or erenumab

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

An additional benefit is not proven.

b) Adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A)

Appropriate comparator therapy for eptinezumab for prophylaxis of migraine:

- Erenumab or fremanezumab or galcanezumab

Extent and probability of the additional benefit of eptinezumab compared to fremanezumab:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine

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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

b) Adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↔	No relevant difference for the benefit assessment
Health-related quality of life	↔	No relevant difference for the benefit assessment
Side effects	↔	No relevant difference 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

1 Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-95) unless otherwise indicated.

∅: There are no usable data for the benefit assessment. n.a.: not assessable

Indirect comparison: Eptinezumab (DELIVER study) vs fremanezumab (FOCUS study) via the bridge comparator placebo.

Mortality

Endpoint Comparator study	**Eptinezumab or fremanezumab**		**Placebo**		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Overall survival/ mortality					
Eptinezumab vs placebo DELIVER (until week 24)	284	0 (0)	287	0 (0)	-
Fremanezumab vs placebo FOCUS (until week 12)	388	0 (0)	195	0 (0)	-
Indirect comparison via bridge comparators[a]:					
Eptinezumab vs fremanezumab					-

Morbidity

Endpoint Comparator study	**Eptinezumab or fremanezumab**		**Placebo**		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Symptomatology: Migraine days/month					
Reduction by ≥ 50%					
Eptinezumab vs placebo DELIVER (until week 12)	284	123 (43.3)	287	38 (13.2)	3.27 [2.36; 4.53] < 0.001[b]
Fremanezumab vs placebo FOCUS (until week 12)	388	144 (37.1[c])	195	19 (9.7[c])	3.82 [2.44; 5.97] < 0.001[d]
Indirect comparison via bridge comparators[a]:					
Eptinezumab vs fremanezumab					-[e]
Reduction by ≥ 75%					

Eptinezumab vs placebo DELIVER (weeks 1-12)	284	47 (16.5)	287	6 (2.1)	7.90 [3.44; 18.1] < 0.001[b]
Fremanezumab vs placebo FOCUS (Week 1-12)	388	46 (11.9[c])	195	5 (2.6[c])	4.64 [1.87; 11.48] < 0.001[d]
Indirect comparison via bridge comparators[a]:					
Eptinezumab vs fremanezumab					-[e]

Endpoint Comparator study	**Eptinezumab or fremanezumab**			**Placebo**			Group difference
	N[h]	Values at the start of the study MV (SD)	Change at week 12 MV (SE/SD)[i]	N[h]	Values at the start of the study MV (SD)	Change at week 12 MV (SE/SD)[i]	MD [95% CI] p value
Symptomatology: Headache days/month							
Any severity (presented additionally)							
Eptinezumab vs placebo DELIVER	284	14.5 (5.7)	-4.6 (0.4)[j]	287	14, (5.9)	-2, (0.4)[j]	-2.7 [-3.4; -1.9] < 0.001[j]
Fremanezumab vs placebo FOCUS	388	14.2 (5.8)	-4.7 (4.6)	195	14.2 (6.1)	-1.3 (4.2)	-3.47 [-4.32; -2.62] < 0.001[k]
Indirect comparison via bridge comparators[a]:							
Eptinezumab vs fremanezumab							-[e]
Health status (EQ-5D VAS)[p]							
Eptinezumab vs placebo DELIVER	n.d.[m]	76.0 (19.0)	2.3 (1.5)[n]	n.d.[m]	73.9 (20.6)	-2.9 (1.5)[n]	5.2 [2.20; 8.29] < 0.001[n]
Fremanezumab vs placebo FOCUS	388	69.6 (21.2)	6.3 (20.1)	195	70.1 (20.1)	1.7 (17.6)	4.22 [1.28; 7.17] 0.005[q]
Indirect comparison via bridge comparators[a]:							
Eptinezumab vs fremanezumab							0.98 [-3.26; 5.22] 0.650

Health-related quality of life

Endpoint Comparator study	**Eptinezumab or fremanezumab**			**Placebo**			Group difference
	N[h]	Values at the start of the study MV (SD)	Change at week 12 MV (SE/SD)[i]	N[h]	Values at the start of the study MV (SD)	Change at week 12 MV (SE/SD)[i]	MD [95% CI] p value
General impairment due to headache (HIT-6)[l]							
Any severity							
Eptinezumab vs placebo DELIVER	n.d.[m]	66.6 (4.7)	-7.1 (0.7)[n]	n.d.[x]	66.3 (4.4)	-3.2 (0.6)[n]	-3.8 [-5.1; -2.6] < 0.001[n]
Fremanezumab vs placebo FOCUS	388	64.2 (4.4)	-6.4 (7.2)	195	64.0 (5.2)	-3.0 (6.2)	-3.37 [-4.45; -2.30] < 0.001[o]
Indirect comparison via bridge comparators[a]:							
Eptinezumab vs fremanezumab							-0.43 [-2.08; 1.22] 0.609
MSQoL[p]							
Role Function-Restrictive							
Eptinezumab vs placebo DELIVER	n.d.[m]	35.7 (17.6)	25.3 (1.9)[n]	n.d.[m]	35.0 (17.0)	14.0 (1.8)[n]	11.3 [7.87; 14.8] < 0.001[n]
Fremanezumab vs placebo FOCUS	388	47.6 (17.4)	18.3 (20.4)	195	47.6 (19.0)	9.7 (17.2)	9.06 [5.77; 12.35] < 0.001[o]
Indirect comparison via bridge comparators[a]:							
Eptinezumab vs fremanezumab							2.24 [-2.54; 7.02] 0.358
Role Function-Preventive							
Eptinezumab vs placebo DELIVER	n.d.[m]	50.2 (21.6)	23.1 (1.7)[n]	n.d.[m]	50.4 (22.0)	11.8 (1.7)[n]	11.3 [8.01; 14.5] < 0.001[n]
Fremanezumab vs placebo FOCUS	388	63.2 (20.4)	14.5 (18.5)	195	64.2 (21.0)	8.6 (17.4)	5.81 [2.82; 8.80] < 0.001[o]
Indirect comparison via bridge comparators[a]:							
Eptinezumab vs fremanezumab							5.49 [1.08; 9.9] 0.015 SMD: 0.2 [0.04; 0.35]

Emotional state							
Eptinezumab vs placebo DELIVER	n.d.[m]	50.1 (24.5)	21.2 (2.0)[n]	n.d.[m]	48.6 (26.7)	9.9 (1.9)[n]	11.3 [7.63; 15.0] < 0.001[n]
Fremanezumab vs placebo FOCUS	388	60.6 (23.9)	16.6 (22.6)	195	60.6 (25.3)	8.1 (21.9)	9.14 [5.52; 12.77] < 0.001[o]
Indirect comparison via bridge comparators[a]:							
Eptinezumab vs fremanezumab							2.16 [-3.01; 7.33]; 0.413

Side effects

Endpoint Comparator study	**Eptinezumab or fremanezumab**		**Placebo**		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Total adverse events (AE) *(presented additionally)*					
Eptinezumab vs placebo DELIVER (until week 24)	284	115 (40.5)	287	112 (39.0)	-
Fremanezumab vs placebo FOCUS (until week 12)	388	208 (53.6)	195	19 (51.8[c])	-
Serious adverse events (SAE)					
Eptinezumab vs placebo DELIVER (until week 24)	284	4 (1.4)	287	4 (1.4)	1.0 [0.3; 4.0] 0.987[f]
Fremanezumab vs placebo FOCUS (until week 12)	388	4 (1.0[c])	195	3 (1.5[c])	0.67 [0.15; 2.96] 0.625[g]
Indirect comparison via bridge comparators[a]:					
Eptinezumab vs fremanezumab					1.49 [0.21; 10.76] 0.691
Therapy discontinuation due to adverse events					
Eptinezumab vs placebo DELIVER (until week 24)	284	0 (0)	287	0 (0)	1.01 [0.06; 16.1] 0.994[f]

Fremanezumab vs placebo FOCUS (until week 12)	388	3 (0.8)	195	2 (1.0[c])	0.75 [0.13; 4.47] 0.829[g]
Indirect comparison via bridge comparators[a]:					
Eptinezumab vs fremanezumab					1.35 [0.05; 35.87] 0.858

a. Indirect comparison according to Bucher
b. RR and CI: Log-binomial model; adjusted for monthly migraine days at the start of the study (≤ 14 days/ > 14 days); p value: Logistic model; adjusted for monthly migraine days at the start of the study (≤ 14 days/ > 14 days) and baseline. Mean percentage change in monthly migraine days was calculated over the 3 4-week intervals. These were replaced, depending on the number of missing diary entries (< 14 days/ ≥ 14 days) and, if applicable, the reason for discontinuation; in the 3 4-week intervals, diary entries were available for ≥ 21 days for > 90% of the patients in both treatment groups.
c. IQWiG calculation
d. RR, CI and p value (unconditional exact test, CSZ method): unadjusted; patients with missing baseline were considered non-responders. For diary entries on ≥ 10 days/month, an extrapolation to 28 days was made, based on the existing data; for diary entries on < 10 days/month, the missing values were updated using LOCF. The extent of replacements made is unclear.
e. No indirect comparison is used for the benefit assessment as the requirement for the certainty of results to perform an adjusted indirect comparison is not met.
f. RR and CI: Log-binomial model; p value: CMH test; each adjusted for monthly headache days at the start of the study (≤ 14 days/ > 14 days). In the case of a zero cell, the correction value 0.5 was added to each cell entry in the corresponding four-field table; for the calculation of the RR as well as the performance of the test, the correction was made per stratum, i.e. only strata with zero cells were adjusted.
g. RR, CI and p value (unconditional exact test, CSZ method): unadjusted
h. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
i. For the DELIVER study, information is provided on the SE, for the FOCUS study on the SD.
j. MV and SE (mean change per treatment group) as well as MD, CI and p value (group comparison): MMRM. These were replaced, depending on the number of missing diary entries (< 14 days/ ≥ 14 days) and, if applicable, the reason for discontinuation; in the 3 4-week intervals, diary entries were available for ≥ 21 days for > 90% of the patients in both treatment groups. Effect represents the difference in mean changes (compared to the start of the study) between the treatment groups in the first 12 weeks of the study.
k. MD, CI and p value (group comparison); according to study documents: MMRM. Patients with missing baseline were excluded from the analysis. For diary entries on ≥ 10 days/month, an extrapolation to 28 days was made, based on the existing data; for diary entries on < 10 days/month, the missing values were updated using LOCF. The extent of replacements made is unclear. Effect represents the difference in mean changes (compared to the start of the study) between the treatment groups in the 12 weeks of the study.
l. Lower scores mean less overall impairment due to headache (scale range 36 to 78), and in direct comparison a negative group difference means an advantage of eptinezumab or fremanezumab. In the indirect comparison, negative effects mean an advantage of eptinezumab.
m. It is unclear how many patients were included in the evaluation; there is only information on the number of patients with assessments at different points in time. According to this, however, more than 90% of the patients must have been included in both treatment groups.
n. MV and SE (mean change per treatment group) as well as MD, CI and p value (group comparison): MMRM. Effect represents the difference in changes (compared to the start of the study) between treatment groups at week 12.
o. MD, CI and p value (group comparison); according to study documents: MMRM. Effect represents the difference in changes (compared to the start of the study) between treatment groups at week 12.
p. Higher values mean a better health status (scale range 0 to 100) or a better health-related quality of life (scale range Role Function-Restrictive 7 to 42, Role Function-Preventive 4 to 24, Emotional Function 3 to 18); in a direct comparison, a positive group difference means an advantage of eptinezumab or fremanezumab. In the indirect comparison, positive effects mean an advantage of eptinezumab.
q. MD, CI and p value (group comparison); according to study documents: ANCOVA. Effect represents the difference in changes (compared to the start of the study) between treatment groups at week 12.

Abbreviations used:

ANCOVA = analysis of covariance; HIT-6 = Headache Impact Test-6; CI = confidence interval; LOCF = Last Observation Carried Forward; MD = mean difference; MMRM = mixed model for repeated measures; MSQoL = Migraine-Specific Quality of Life; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; RR = relative risk; SD = standard deviation; SE = standard error; SMD = standard mean difference; VAS = visual analogue scale; vs = versus

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

a) Adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine

Approx. 1,598,600 to 1,628,400 patients

b) Adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A)

Approx. 15,700 to 16,800 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 Vyepti (active ingredient: eptinezumab) at the following publicly accessible link (last access: 11 January 2023):

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

Treatment with eptinezumab should only be initiated and monitored by doctors experienced in migraine therapy.

4. Treatment costs

Annual treatment costs:

a) Adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Eptinezumab	€ 5,416.02 -€ 16,248.07
Appropriate comparator therapy:	
Amitriptyline	€ 58.33 - € 95.78

Designation of the therapy	Annual treatment costs/ patient
Flunarizine	€ 48.84 – € 76.97[2]
Metoprolol	€ 43.25 - € 61.39
Propranolol	€ 122.71 - € 184.07
Topiramate	€ 277.07
Clostridium botulinum toxin type A[3]	€ 3,372.03
Erenumab	€ 3,794.31

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2023)

Costs for additionally required SHI services: not applicable

Other SHI benefits: not applicable

b) Adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Eptinezumab	€ 5,416.02 -€ 16,248.07
Appropriate comparator therapy:	
Erenumab	€ 3,794.31
Fremanezumab	€ 5,035.20
Galcanezumab	€ 5,301.32

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2023)

Costs for additionally required SHI services: not applicable

Other SHI benefits: not applicable

5. 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 Eptinezumab

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with eptinezumab for the prophylaxis of migraine in adults

2 In accordance with the information provided in the product information, a limited treatment duration of six months is assumed for flunarizine. Notwithstanding this, the costs may be higher if treatment with flunarizine is started again at a later date.
3 According to the marketing authorisation only for chronic migraine.

who have at least 4 migraine days per month on the basis of the marketing authorisation granted under Medicinal Products Act:

a) Adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine

   – No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b) Adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A)

   – No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 February 2023.

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

Berlin, 16 February 2023

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

Prof. Hecken