Resolution

Gemeinsamer Bundesausschuss

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 Fremanezumab

of 7 November 2019

At its session on 7 November 2019, 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:

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

Fremanezumab

Resolution of: 7 November 2019
Entry into force on: 7 November 2019
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 28 March 2019):

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

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

a) Untreated adult patients and patients who have responded inadequately, are unable to tolerate or are unsuitable for at least one prophylactic medication

Appropriate comparator therapy:

- Metoprolol or propranolol or flunarizine or topiramate or amitriptyline, taking into account marketing authorisation and the previous therapy

Extent and probability of the additional benefit of fremanezumab compared with the appropriate comparator therapy:

Additional benefit not proven

b) Adult patients who are not responsive to or or are unsuitable for or do not tolerate the medicinal therapies/active ingredient classes metoprolol, propranolol, flunarizine, topiramate, and amitriptyline

Appropriate comparator therapy:

- Valproic acid[1] or Clostridium botulinum toxin type A[2]

Extent and probability of the additional benefit of fremanezumab compared with the appropriate comparator therapy:

Additional benefit not proven

[1] According to Annex VI to Section K of the Pharmaceuticals Directive: if treatment with any other authorised medicinal product has not been successful or is contraindicated.
[2] According to the marketing authorisation for chronic migraines.

c) Adult patients who are not responsive to or are unsuitable for or do not tolerate any of the aforementioned medicinal therapies/active ingredient classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid or Clostridium botulinum toxin type A)

Appropriate comparator therapy:

- Best supportive care

Extent and probability of the additional benefit of fremanezumab compared with best supportive care:

Hint for a considerable additional benefit

Study results according to endpoints:

a) Untreated adult patients and patients who have responded inadequately, are unable to tolerate or are unsuitable for at least one prophylactic medication

No relevant data were submitted.

b) Adult patients who are not responsive to or are unsuitable for or do not tolerate the medicinal therapies/active ingredient classes metoprolol, propranolol, flunarizine, topiramate, and amitriptyline

No relevant data were submitted.

c) Adult patients who are not responsive to or are unsuitable for or do not tolerate any of the aforementioned medicinal therapies/active ingredient classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid or Clostridium botulinum toxin type A)

Results of the RCT FOCUS[3]: Fremanezumab + BSC vs placebo + BSC at week 12

FOCUS trial **Endpoint category** **Endpoint**	**Fremanezumab + BSC**		**Placebo + BSC**		**Fremanezumab + BSC vs placebo + BSC**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value[a]**
Mortality					
Overall mortality	388	0 (0)	195	0 (0)	---

[3] Data from the dossier evaluation of the IQWiG (A19-44) and the addendum (A19-82) unless otherwise indicated.

FOCUS trial Endpoint category Endpoint	Fremanezumab + BSC		Placebo + BSC		Fremanezumab + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Morbidity					
Symptomatology					
Migraine days/month[b]					
Reduction by ≥ 50 %	388	144 (37)	195	19 (10)	3.82 [2.44; 5.97]; < 0.001
Reduction by ≥ 75 %	388	46 (12)	195	5 (3)	4.64 [1.87; 11.48]; < 0.001
Reduction by 100 %	388	4 (1)	195	0 (0)	4.54 [0.25; 83.91]; 0.161

FOCUS trial Endpoint category Endpoint	Fremanezumab + BSC			Placebo + BSC			Fremanezumab + BSC vs placebo + BSC
	N[d]	Values at start of study MV (SD)	Change at end of study (SD)	N[d]	Values at start of study MV (SD)	Change at end of study MV (SD)	MD [95 % CI]; p value
Headache days/month[c] (reduction by ≥ 50 %, additionally shown)	No data available.						
Headache days/month, all severities[e] (additionally shown)	388	14.2 (5.8)	-4.72 (4.59)	195	14.2 (6.1)	-1.28 (4.19)	-3.47 [-4.32; -2.62]; < 0.001
Health status (EQ-5D VAS)[f]	388	69.6 (21.2)	6.28 (20.14)	195	70.1 (20.1)	1.72 (17.6)	4.22 [1.28; 7.17]; 0.005 Hedges' g: 0.24 [0.06; 0.41]
Health-related quality of life							
General impairment due to headache (HIT-6)[g]	388	64.2 (4.4)	-6.43 (7.16)	195	64.0 (5.2)	-2.96 (6.18)	-3.37 [-4.45; -2.30]; < 0.001 Hedges' g: -0.57 [-0.74; -

FOCUS trial Endpoint category Endpoint	Fremanezumab + BSC			Placebo + BSC			Fremanezumab + BSC vs placebo + BSC
	N[d]	Values at start of study MV (SD)	Change at end of study (SD)	N[d]	Values at start of study MV (SD)	Change at end of study MV (SD)	MD [95 % CI]; p value
							0.39]
Migraine-Specific Quality of Life (MSQoL)[h]							
Restriction of role function	388	47.6 (17.4)	18.33 (20.44)	195	47.6 (19.0)	9.74 (17.15)	9.06 [5.77; 12.35]; < 0.001 Hedges' g: 0.44 [0.27; 0.62]
Prevention of role function	388	63.2 (20.4)	14.51 (18.52)	195	64.2 (21.0)	8.56 (17.35)	5.81 [2.82; 8.80]; < 0.001 Hedges' g: 0.33 [0.16; 0.50]
Emotional state	388	60.6 (23.9)	16.55 (22.6)	195	60.6 (25.3)	8.1 (21.88)	9.14 [5.52; 12.77]; < 0.001 Hedges' g: 0.38 [0.204; 0.55]

FOCUS trial Endpoint category Endpoint	Fremanezumab + BSC		Placebo + BSC		Fremanezumab + BSC vs placebo + BSC
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value[a]
Side effects					
AE (additionally shown)	388[i]	208 (53,61[i])	195	101 (52)	–
SAE	388[i]	4 (1[i])	195	3 (1)	0.67 [0.15; 2.96]; 0.625
Discontinuation because of AE	388[i]	3 (0.8[i])	195	2 (1)	0.75 [0.13; 4.47]; 0.829

a: IQWiG's own calculation (exact unconditional test, CSZ method according to Martin Andrés *et al.*, 1994).
b: Defined as a calendar day on which a patient documented a migraine headache or a probable migraine headache for ≥ 4 consecutive hours or documented taking migraine-specific headache medication.
c: Defined as a calendar day on which ≥ 4 consecutive hours of headache of any severity occurred or on which taking migraine-specific headache medication was necessary (documented in electronic diary).
d: Number of patients who were taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of the study can be based on other patient figures.
e: Defined as a calendar day on which ≥ 4 consecutive hours of headache of any severity occurred or on which taking migraine-specific headache medication was necessary (documented in electronic diary).

f: Higher values indicate a better health status; a positive group difference corresponds to an advantage for fremanezumab.
g: Higher values indicate a deterioration of the general impairment due to headache; a negative group difference indicates an advantage for fremanezumab.
f: Higher values indicate improved health-related quality of life; a positive group difference corresponds to an advantage for fremanezumab.
i: Incorrect information in the submitted documents, IQWiG's own analysis.

BSC: best supportive care; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HIT-6: Headache Impact Test-6; CI: confidence interval; MD: mean difference; MMRM: mixed model with repeated measurements; MSQoL: migraine-specific quality of life questionnaire; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

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

a) Untreated adult patients and patients who have responded inadequately, are unable to tolerate or are unsuitable for at least one prophylactic medication

approx. 1,428,000–1,445,000 patients

b) Adult patients who are not responsive to or are unsuitable for or do not tolerate the medicinal therapies/active ingredient classes metoprolol, propranolol, flunarizine, topiramate, and amitriptyline

approx. 1,400–11,000 patients

c) Adult patients who are not responsive to or are unsuitable for or do not tolerate any of the aforementioned medicinal therapies/active ingredient classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid or Clostridium botulinum toxin type A)

approx. 14,000–15,000 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 Ajovy® (active ingredient: fremanezumab) at the following publicly accessible link (last access: 11 September 2019):

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

Treatment with fremanezumab may only be initiated and monitored by specialists who are experienced in the diagnosis and treatment of patients with migraine.

4. Treatment costs

Annual treatment costs:

a) Untreated adult patients and patients who have responded inadequately, are unable to tolerate or are unsuitable for at least one prophylactic medication

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fremanezumab	€ 7,652.32
Appropriate comparator therapy:	
Amitriptyline	€ 58.11–103.00
Flunarizine	€ 48.71–76.83[4]
Metoprolol	€ 43.00–61.14
Propranolol	€ 122.20–183.30
Topiramate	€ 276.85

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2019

b) Adult patients who are not responsive to or are unsuitable for or do not tolerate the medicinal therapies/active ingredient classes metoprolol, propranolol, flunarizine, topiramate, and amitriptyline

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fremanezumab	€ 7,652.32
Appropriate comparator therapy:	
Clostridium botulinum toxin type A[2]	€ 3,326.15
Valproic acid[1]	€ 73.66–220.97

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2019

[4] According to the information provided in the product information, flunarizine is administered for a limited period of six months. Nevertheless, the costs may be higher if a new treatment with flunarizine is started at a later date.

c) Adult patients who are not responsive to or are unsuitable for or do not tolerate any of the aforementioned medicinal therapies/active ingredient classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid or Clostridium botulinum toxin type A)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fremanezumab	€ 7,652.32
Best supportive care	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2019

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 7 November 2019.

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

Berlin, 7 November 2019

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

Prof Hecken