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 Erenumab (Reassessment due to New Scientific Knowledge (Prophylaxis of Migraine))

of 21 October 2021

At its session on 21 October 2021, the Federal Joint Committee (G-BA) resolved to amend Annex XII of 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 2 May 2019 (BAnz AT 11.06.2019 B2) and the publication of the resolution of 19 September 2019 (BAnz AT 15.10.2019 B3), as follows:

I. The information concerning the active ingredient erenumab (prophylaxis of migraine) as set out in the resolution of 2 May 2019 (BAnz AT 11.06.2019 B2) is amended as follows:

1. Number 1, "Additional benefit of the medicinal product in relation to the appropriate comparator therapy", is amended as follows:

   a) The section under the heading "Additional benefit of the medicinal product in relation to the appropriate comparator therapy" is amended as follows:

      aa) The sections following points a) and b) are replaced by the following section a):

      "a) Adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine

      Appropriate comparator therapy for prophylaxis of migraine:

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

      Extent and probability of the additional benefit of erenumab compared to topiramate:

      Hint for a considerable additional benefit".

      bb) the existing section after point c) becomes section b).

b) The section under the heading “Study results according to endpoints” is amended as follows:

aa) After the heading “Study results according to endpoints”, the statement in footnote 3 “[3]Data from the dossier evaluation of the IQWiG (A-18-71) unless otherwise indicated.” is replaced by the following:

“[3]Data from the dossier assessment of the IQWiG (A18-71 and A21-58) unless otherwise indicated”.

bb) The sections following points a) and b) are replaced by the following section a):

"a) Adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine

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	↑	Advantages in symptomatology (migraine days per month).
Health-related quality of life	↑	Advantages in the HIT-6 as well as the SF-36 (PCS + MCS).
Side effects	↑	Advantage in discontinuation due to AEs; no overall advantage or disadvantage in overall rates.
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		

HER-MES study: RCT erenumab vs topiramate (24 week data)

Study HER-MES Endpoint	Erenumab		Topiramate		Erenumab vs Topiramate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Mortality					
Overall mortality	388	0 (0)	388	0 (0)	---

Study HER-MES Endpoint Scale	Erenumab		Topiramate		Erenumab vs Topiramate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a] Absolute difference (AD)[4]
Morbidity					
Symptomatology: Migraine days/month					
Reduction by ≥ 50% over the last 3 months	388[b]	215 (55.4)	388[b]	121 (31.2)	1.78 [1.50; 2.11]; <0.001 AD: 24.2%
Reduction by ≥ 50% over the 1st month	388[c]	147 (37.9)	388[c]	86 (22.2)	1.71 [1.36; 2.14]; <0.001 AD: 15.7%

4 Only in the case of significant results

Study HER-MES Endpoint Scale	Erenumab		Topiramate		Erenumab vs Topiramate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a] Absolute difference (AD)[4]
Health-related quality of life					
general impairment due to headache (HIT-6)[d]					
Improvement by ≥ 6.3 points (corresponds to 15%)	388[e]	251 (64.7)	388[e]	178 (45.9)	1.41 [1.24; 1.61]; <0.001 AD: 18.8%
Improvement by ≥ 5 points	388[e]	280 (72.2)	388[e]	209 (53.9)	1.34 [1.20; 1.50]; <0.001 AD: 18.3%
SF-36v2[f]					
Physical component score (PCS)[g]: Improvement by ≥ 9.4 points (corresponds to 15%)	388[h]	93 (24.0)	388[h]	77 (19.8)	1.21 [0.92; 1.58]; 0.166
Mental component score (MCS)[i]: Improvement by ≥ 9.4 points (corresponds to 15%)	388[h]	45 (11.6)	388[h]	31 (8.0)	1.45 [0.94; 2.24]; 0.093
PCS: Improvement by ≥ 5 points	388[h]	185 (47.7)	388[h]	145 (37.4)	1.28 [1.08; 1.51]; 0.004 AD: 10.3%
MCS: Improvement by ≥ 5 points	388[h]	98 (25.3)	388[h]	65 (16.8)	1.51 [1.14; 2.00]; 0.004 AD: 8.5%

Study HER-MES Endpoint	Erenumab		Topiramate		Erenumab vs Topiramate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a] Absolute difference (AD)[4]
Side effects					
AEs (presented additionally)	388	338 (87.1)	388	361 (93.0)	–
SAEs	388	10 (2.6)	388	19 (4.9)	0.53 [0.25; 1.12]; 0.095
Discontinuation because of AEs	388	41 (10.6)	388	151 (38.9)	0.27 [0.20; 0.37]; <0.001 AD: 28.3%
Nervous system disorders (SOC, AE), including:	388	96 (24.7)	388	253 (65.2)	0.38 [0.31; 0.46]; <0.001 AD: 40.5%
Paraesthesia (PT, AE)	388	17 (4.4)	388	159 (41.0)	0.11 [0.07; 0.17]; <0.001 AD: 36.6%
Attention deficit (PT, AE)	388	18 (4.6)	388	63 (16.2)	0.29 [0.17; 0.47]; < 0.001 AD: 11.6%
Vertigo (PT, AE)	388	28 (7.2)	388	60 (15.5)	0.47 [0.30; 0.71]; <0.001 AD: 8.3%
Nausea (PT, AE)	388	36 (9.3)	388	71 (18.3)	0.51 [0.35; 0.74]; <0.001 AD: 9.0%
Constipation (PT, AE)	388	48 (12.4)	388	12 (3.1)	4.00 [2.16; 7.41]; <0.001 AD: 9.3%

Study HER-MES Endpoint	Erenumab		Topiramate		Erenumab vs Topiramate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a] Absolute difference (AD)[4]
Fatigue (PT, AE)	388	44 (11.3)	388	74 (19.1)	0.59 [0.42; 0.84]; 0.003 AD: 7.8%
Decreased appetite (PT, AE)	388	8 (2.1)	388	40 (10.3)	0.20 [0.09; 0.42]; <0.001 AD: 8.2%

a. Wald test
b. The values of 10 (2.6%) patients in the erenumab arm and 17 (4.4%) patients in the topiramate arm were replaced by non-responder imputation.
c. The values of 5 (1.3%) patients in the erenumab arm and 3 (0.8%) patients in the topiramate arm were replaced by non-responder imputation.
d. Patients with an improvement of ≥ 6.3 points (corresponds to 15% of the scale range)
e. The values of 24 (6.2%) patients in the erenumab arm and 30 (7.7%) patients in the topiramate arm were replaced by non-responder imputation.
f. no information on sub-scales available
g. Patients with an improvement of ≥ 9.4 points (corresponds to 15% of the scale range)
h. The values of 25 (6.4%) patients in the erenumab arm and 33 (8.5%) patients in the topiramate arm were replaced by non-responder imputation.
i. Patients with an improvement of ≥ 9.6 points (corresponds to 15% of the scale range)

HIT-6: Headache Impact Test-6; CI: confidence interval; MCS: Mental Component Summary; n: number of patients with (at least 1) event; MCS: Mental Component Summary; N: number of patients evaluated; N: number of patients evaluated; PCS: physical component summary; PT: preferred term; RCT: randomised controlled study; RR: relative risk; SF-36v2: Short Form-36 Health Survey Version 2; SOC: system organ class; SAE: serious adverse event; AE: adverse event

“.

cc) The existing section after c) becomes section b).

2. Number 2, “Number of patients or demarcation of patient groups eligible for treatment,” is amended as follows:

a) The sections following points a) and b) are replaced by the following section a):

"a) Adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine

approx. 1,540,100 - 1,568,800 patients".

b) The existing section after c) becomes section b).

3. In number 3, "Requirements for quality-assured application", before the words "Initiation and monitoring of", the information "(last access: 28 February 2019): https://www.ema.europa.eu/en/documents/product-information/aimovig-epar-product-information_en.pdf" is replaced by the following:

"(last access: 9 August 2021): https://www.ema.europa.eu/en/documents/product-information/aimovig-epar-product-information_en.pdf ".

4. Number 4, "Treatment costs", is replaced by the following:

a) The sections following points a) and b) are replaced by the following section a):

"(a) Adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Erenumab	€ 5,992.22
Appropriate comparator therapy:	
Amitriptyline	€ 58.33 - € 95.74
Flunarizine	€ 48.83 - € 76.95[5]
Metoprolol	€ 43.22 - € 61.36
Propranolol	€ 122.64 - € 183.96
Topiramate	€ 277.07
Clostridium botulinum toxin type A[6]	€ 3,413.23

5 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.

6 According to the marketing authorisation only for chronic migraine.

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 October 2021)

Costs for additionally required SHI services: not applicable".

b) the existing section after point c) becomes section b).

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 21 October 2021.

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

Berlin, 21 October 2021

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

Prof. Hecken