Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V – Erenumab

of 2 May 2019

At its session on 2 May 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 erenumab as follows:

Erenumab

Resolution of: 2 May 2019
Entry into force on: 2 May 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 26 July 2018):

Aimovig 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 to at least one prophylactic medication or 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 erenumab compared with the appropriate comparator therapy:

Additional benefit not proven.

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

Appropriate comparator therapy:

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

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

Additional benefit not proven.

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

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.

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

Hint for a considerable additional benefit

Study results according to endpoints[3]:

a) Untreated adult patients and patients who have responded inadequately to at least one prophylactic medication or 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 LIBERTY study: RCT erenumab + BSC vs placebo + BSC at week 12

LIBERTY study Endpoint category Endpoint	Erenumab + BSC		Placebo + BSC		Erenumab + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Mortality					
Overall mortality	86	0 (0)	104	0 (0)	---

LIBERTY study Endpoint category Endpoint	Erenumab + BSC		Placebo + BSC		Erenumab + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Morbidity					
Symptomology					
Migraine days/month, Reduction by ≥ 50%	86	26 (30.2)	104	14 (13.5)	2.25 [1.25; 4.03]; 0.005 [a]

[3] Data from the dossier evaluation of the IQWiG (A18-71) unless otherwise indicated.

LIBERTY study Endpoint category Endpoint	Erenumab + BSC		Placebo + BSC		Erenumab + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Migraine attacks/month, reduction by ≥ 50% (additionally shown)	86	20 (23.3)	104	12 (11.5)	2.02 [1.05; 3.88]; 0.033[a]

LIBERTY study Endpoint category Endpoint	Erenumab + BSC vs placebo + BSC			Erenumab + BSC vs placebo + BSC			Erenumab + BSC vs placebo + BSC
	N[b]	Values at start of study MV (SD)	Change at week 12 MV[c] (SE)	N[b]	Values at start of study MV (SD)	Change at week 12 MV[c] (SE)	MD [95% CI]; p value[d]
Morbidity							
Health status (*EQ-5D VAS*)[e]	86	79.66 (16.80)	2.1 (2.12)	104	77.50 (19.92)	0.76 (1.81)	1.35 [−4.18; 6.88]; 0.630
Physical function (MPFID[f])							
Effects on daily activities	86	13.53 (8.13)	−3.17 (0.95)	104	13.98 (8.85)	0.58 (0.81)	−3.74 [−6.09; −1.39]; 0.002 Hedges' g[g]: −0.45 [−0.74; −0.16]
Physical impairment	86	12.56 (9.30)	−2.05 (0.96)	104	13.03 (9.61)	1.63 (0.82)	−3.68 [−6.08; −1.28]; 0.003 Hedges' g[g]: −0.44 [−0.73; −0.15]
Overall influence on daily activities	86	13.92 (8.37)	−2.73 (1.00)	104	14.45 (8.96)	1.01 (0.86)	−3.74 [−6.25; −1.24]; 0.004 Hedges' g[g]: −0.42 [−0.71; −0.14]
Work productivity and activity impairment (WPAI headache[f])							
Absenteeism[h, i]	61	8.88 (14.29)	−2.68 (1.67)	75	7.26 (14.89)	1.21 (2.26)	−3.89 [−9.47; 1.69]; 0.170
Presenteeism[h, j]	61	36.23 (24.09)	−11.00 (3.10)	74	33.65 (24.08)	−2.11 (3.18)	−8.88 [−17.50; −0.27]; 0.043 Hedges' g[e]: −0.35 [−0.69; −0.01]

LIBERTY study Endpoint category Endpoint	Erenumab + BSC vs placebo + BSC			Erenumab + BSC vs placebo + BSC			Erenumab + BSC vs placebo + BSC
	N[b]	Values at start of study MV (SD)	Change at week 12 MV[c] (SE)	N[b]	Values at start of study MV (SD)	Change at week 12 MV[c] (SE)	MD [95% CI]; p value[d]
Overall restriction (absenteeism + presenteeism)[h, k]	61	42.24 (22.81)	−12.61 (3.18)	74	36.26 (25.64)	−1.96 (3.50)	−10.65 [−19.79; −1.51]; 0.023 Hedges' g[e]: −0.34 [−0.68; 0.00]
Activity impairment[k]	85	42.35 (23.84)	−7.65 (2.71)	104	37.12 (22.63)	0.08 (2.38)	−7.74 [−14.55; −0.93]; 0.026 Hedges' g[e]: −0.32 [−0.47; −0.22]

LIBERTY study Endpoint category Endpoint	Erenumab + BSC vs placebo + BSC		Erenumab + BSC vs placebo + BSC		Erenumab + BSC vs placebo + BSC
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value
Health-related quality of life [l]					
General impairment because of headache (HIT-6)					
Improvement by ≥ 5 points	86	44 (51.2)	104	28 (26.9)	1.90 [1.30; 2.77]; < 0.001[a]
Side effects					
AE (additionally shown)	86	52 (60.5)	104	61 (58.7)	–
SAE	86	2 (2.3)	104	1 (1.0)	2.42 [0.22; 26.22]; 0.592[a]
Discontinuation because of AE	86	0 (0)	104	2 (1.9)	–[m]; 0.228[a]

a: Own calculation by the IQWiG, exact unconditional test (CSZ method according to Martin Andrés et al., 1994).
b: 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 study (at other times, if necessary) can be based on other patient figures.
c: Unless indicated otherwise, MMRM evaluation of the ITT population
d: Effect, confidence interval, and p value Mixed model with repeated measurements (MMRM) adjusted for baseline value, severity of disease, round, and interaction of treatment and round
e: Higher values mean a better health status; a positive group difference corresponds to an advantage for erenumab
f: Higher values mean a greater impairment; a negative group difference corresponds to an advantage

for erenumab
g: Own calculation of the IQWiG
h: Evaluation only includes patients in an employment relationship
i: Absence from work because of impairment because of headache, hours absent in%.
j: Impairment because of headache at work, working hours with impairment in%.
k: In %
l: Deviating from the procedure of the pharmaceutical company, the endpoints of morbidity collected via ~~HIT-6~~, MPFID, and EQ-5D VAS are assigned.
m: no representation of effect estimation and CI because not informative

BSC: Best supportive care; CI: confidence interval; N Number of patients evaluated; RCT: randomised controlled study; BSC: Best supportive care; EQ-5D: European Quality of Life Group 5 Dimensions; HIT-6: Headache Impact Test-6; ITT: Intention to Treat; CI: Confidence Interval; MD: mean difference; MMRM: mixed model with repeated measurements; MPFID: Migraine Physical Function Impact Diary; MV: mean value; n: number of patients with (at least 1) event; N: Number of patients evaluated; RCT: Randomised Controlled Study; RR: Relative Risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus; WPAI: Work Productivity and Activity Impairment

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

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

approx. 2,365,000–2,454,000 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. 10,000–11,000 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 Aimovig® (active ingredient: Erenumab) at the following publicly accessible link (last access: 28 February 2019):

https://www.ema.europa.eu/documents/product-information/aimovig-epar-product-information_de.pdf

Treatment with erenumab 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 to at least one prophylactic medication, or 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:	
Erenumab	€ 8,290.01–16,580.03
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 April 2019)

b) Adult patients who are not responsive to or are unsuitable for 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:	
Erenumab	€ 8,290.01–16,580.03
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 April 2019)

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)

[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.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Erenumab	€ 8,290.01–16,580.03
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 April 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 2 May 2019.

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

Berlin, 2 May 2019

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

Prof Hecken