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 Galcanezumab

of 19 September 2019

At its session on 19 September 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 galcanezumab as follows:

Galcanezumab

Resolution of: 19 September 2019
Entry into force on: 19 September 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 14 November 2018):

Emgality is indicated for the 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 galcanezumab compared with the appropriate comparator therapy:

Additional benefit not proven.

b) Adult patients who are not responsive to or are unsuitable to 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 galcanezumab 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 to 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 galcanezumab 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 to 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 to 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 from three double-blind RCT studies: The EVOLVE-1 and EVOLVE-2 studies investigated patients with episodic migraine; the REGAIN study investigated patients with chronic migraine; intervention: Galcanezumab + BSC vs placebo + BSC.

[3] Data from the dossier evaluation of the IQWiG (A19-28) and the addendum of the IQWiG unless otherwise indicated.

Mortality

Endpoint	Galcanezumab + BSC		Placebo + BSC		Galcanezumab + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall mortality					
EVOLVE-1	*7*	*0 (0)*	*10*	*0 (0)*	-
EVOLVE-2	*27*	*0 (0)*	*28*	*0 (0)*	-
EVOLVE-1/-2[b]	34	0 (0)	38	0 (0)	-
REGAIN	36	0 (0)	110	0 (0)	-

Morbidity

Endpoint	Galcanezumab + BSC		Placebo + BSC		Galcanezumab + BSC vs placebo + BSC
	N	Mean proportion of patients with improvement % [95% CI]	N	Mean proportion of patients with improvement % [95% CI]	RR [95% CI]; p value[c]
Symptomology: Migraine days/month, reduction by ≥ 50% compared with baseline phase, averaged over treatment period[d]					
EVOLVE-1	*7*	*42.86 [27.84; 59.31]*	*10*	*15.00 [7.55; 27.61]*	*2.86 [1.34; 6.09]; 0.010*
EVOLVE-2	*27*	*65.43 [57.61; 72.50]*	*28*	*14.29 [9.67; 20.59]*	*4.58 [3.08; 6.81]; < 0.001*
EVOLVE-1/-2[e]	34	60.88 [53.85; 67.49]	38	14.22 [10.20; 19.50]	4.28 [3.03; 6.04]; < 0.001
REGAIN	36	41.67 [35.22; 48.41]	110	10.00 [7.92; 12.56]	4.17 [3.15; 5.51]; < 0.001
Total[f]					4.21 [3.39; 5.24]; < 0.001

Endpoint	Galcanezumab + BSC		Placebo + BSC		Galcanezumab + BSC vs placebo + BSC
	N	Mean proportion of patients with improvement % [95% CI]	N	Mean proportion of patients with improvement % [95% CI]	RR [95% CI]; p value[c]
Symptomology: Migraine days/month, reduction by ≥ 75% compared with baseline phase, averaged over treatment period[d]					
EVOLVE-1	*7*	*26.19 [14.38; 42.85]*	*10*	*6.67 [2.32; 17.71]*	*3.93 [1.22; 12.64]; 0.025*
EVOLVE-2	*27*	*41.36 [33.87; 49.27]*	*28*	*2.98 [1.22; 7.09]*	*13.90 [5.63; 34.29]; < 0.001*
EVOLVE-1/-2[e]	34	38.16 [31.63; 45.16]	38	3.90 [2.02; 7.42]	9.78 [4.97; 19.24]; < 0.001
REGAIN	36	9.26 [6.03; 13.96]	110	2.42 [1.48; 3.94]	3.82 [2.00; 7.28]; < 0.001
Total[f]	Heterogeneity: Q = 3.88, df = 1, p = 0.049, I^2 = 74.2%				
Symptomology: Migraine days / month, reduction by 100% compared with baseline phase, averaged over treatment period[d]					
EVOLVE-1	*7*	*9.52 [3.32; 24.40]*	*10*	*6.67 [2.32; 17.71]*	*1.43 [0.34; 6.06]; 0.606*
EVOLVE-2	*27*	*19.75 [14.21; 26.78]*	*28*	*0.00 [no data available[g]]*	*no data available[g,h]*
EVOLVE-1/-2[e]	34	17.64 [12.93; 23.61]	38	1.75 [0.65; 4.65]	10.06 [3.58; 28.29]; < 0.001
REGAIN	36	*0,00 [no data available]*	110	0.30 [0.07; 1.26]	*no data available[g,i]*
Total[f]					-

Endpoint	Galcanezumab + BSC		Placebo + BSC		Galcanezumab + BSC vs placebo + BSC
	N	Mean proportion of patients with improvement % [95% CI]	N	Mean proportion of patients with improvement % [95% CI]	RR [95% CI]; p value[c]
Symptomology: Headache days / month, reduction by ≥ 50% compared with baseline phase, averaged over treatment period[d] (additionally shown)					
EVOLVE-1	*7*	*38.10 [23.82; 54.78]*	*10*	*16.67 [8.72; 29.50]*	*2.29 [1.09; 4.81]; 0.032*
EVOLVE-2	*27*	*46.30 [28.59; 54.18]*	*28*	*13.10 [8.70; 19.25]*	*3.54 [2.29; 5.45]; < 0.001*
EVOLVE-1/-2[e]	34	44.61 [37.81; 51.61]	38	14.03 [10.04; 19.27]	3.18 [2.21; 4.57]; < 0.001
REGAIN	36	35.19 [29.06; 41.84]	110	8.79 [6.84; 11.22]	4.00 [2.94; 5.45]; < 0.001
Total[f]					3.63 [2.87; 4.60]; < 0.001

Endpoint	Galcanezumab + BSC			Placebo + BSC			Galcanezumab + BSC vs placebo + BSC
	N[j]	Values at start of study MV (SD)	Change[k] MV (SE)[l]	N[j]	Values at start of study MV (SD)	Change[k] MV (SE)[l]	MD [95% CI]; p value[l]
Symptomology: Headache days/month (additionally shown)							
EVOLVE-1	*7*	*10.2 (2.62)*	*−2.23 (1.64)*	*10*	*10.3 (3.29)*	*−1.30 (1.27)*	*−0.92 [−5.47; 3.63]; 0.673*
EVOLVE-2	*27*	*10.7 (3.42)*	*−3.35 (0.92)*	*28*	*10.3 (2.94)*	*−0.12 (1.02)*	*−3.23 [−5.63; −0.83]; 0.010*
EVOLVE-1/-2[m]	34	10.6 (3.25)	−3.63 (0.97)	38	10.3 (2.99)	−0.86 (0.85)	−2.77 [−4.82; −0.71]; 0.009
REGAIN	36	21.8 (4.85)	−6.41 (1.00)	109	21.8 (3.94)	−1.72 (0.69)	−4.69 [−6.67; −2.72]; < 0.001
Total[f]							−3.77 [−5.19; −2.34]; < 0.001

Endpoint	Galcanezumab + BSC			Placebo + BSC			Galcanezumab + BSC vs placebo + BSC
	N[j]	Values at start of study[n] MV (SD)	Change[k] MV (SE)[l]	N[j]	Values at start of study[n] MV (SD)	Change[k] MV (SE)[l]	MD [95% CI]; p value[l]
Symptomology: Migraine hours/month (additionally shown)							
EVOLVE-1	*7*	*67.7 (64.23)*	*−28.70 (7.59)*	*10*	*55.2 (36.05)*	*2.84 (6.58)*	*−31.54 [−53.15; −9.93]; 0.007*
EVOLVE-2	*27*	*51.7 (30.94)*	*−29.21 (6.60)*	*28*	*62.5 (46.11)*	*−1.02 (6.98)*	*−28.19 [−46.95; −9.42]; 0.005*
EVOLVE-1/-2[m]	34	55.0 (39.34)	−27.25 (6.45)	38	60.6 (43.34)	0.33 (5.74)	−27.58 [−41.76; −13.40]; < 0.001
REGAIN	36	144.8 (99.73)	−60.32 (11.02)	109	144.1 (90.61)	−3.06 (7.55)	−57.25 [−79.23; −35.28]; < 0.001
Total	Heterogeneity: Q = 4.94, df = 1, p = 0.026, I^2 = 79.8 %						
Severity of the disease (PGI-S[o])							
EVOLVE-1	*7*	*4.7 (1.38)*	*−1.28 (0.54)*	*8*	*5.0 (0.82)*	*−0.59 (0.45)*	*−0.69 [−2.30; 0.93]; 0.373*
EVOLVE-2	*26*	*4.1 (1.40)*	*−0.93 (0.23)*	*21*	*4.8 (0.97)*	*−0.92 (0.27)*	*−0.01 [−0.68; 0.66]; 0.975*
EVOLVE-1/-2[m]	33	4.2 (1.39)	−0.87 (0.25)	29	4.9 (0.92)	−0.68 (0.25)	−0.19 [−0.79; 0.41]; 0.527
REGAIN	30	5.0 (1.11)	−0.62 (0.24)	96	5.0 (1.22)	−0.50 (0.15)	−0.12 [−0.61; 0.37]; 0.632
Total							−0.15 [−0.53; 0.23]; 0.445

Endpoint	Galcanezumab + BSC			Placebo + BSC			Galcanezumab + BSC vs placebo + BSC
	N[j]	Values at start of study[n] MV (SD)	Change[k] MV (SE)[l]	N[j]	Values at start of study[n] MV (SD)	Change[k] MV (SE)[l]	MD [95% CI]; p value[l]
Health status – Change of migraine condition during therapy (PGI-I[o])							
EVOLVE-1	*7*	–	*2.55 (0.38)*	*10*	–	*3.52 (0.29)*	*−0.97 [−2.03; 0.09]; 0.069*
EVOLVE-2	*27*	–	*2.31 (0.19)*	*26*	–	*3.40 (0.22)*	*−1.09 [−1.64; −0.55]; < 0.001*
EVOLVE-1/-2[m]	34	–	2.25 (0.21)	36	–	3.37 (0.19)	−1.12 [−1.60; −0.64]; < 0.001
REGAIN	34	–	2.94 (0.18)	102	–	3.63 (0.12)	−0.69 [−1.04; −0.34]; < 0.001
Total							−0.84 [−1.12; −0.56]; < 0.001 Hedges' g [95% CI][p]: −0.87 [−1.17; −0.57]

Health-related quality of life

Endpoint	Galcanezumab + BSC			Placebo + BSC			Galcanezumab + BSC vs placebo + BSC
	N[j]	Values at start of study[n] MV (SD)	Change[k] MV (SE)[l]	N[j]	Values at start of study[n] MV (SD)	Change[k] MV (SE)[l]	MD [95% CI]; p value[l]
MSQ[q]							
Role Function-Restrictive Domain							
EVOLVE-1	*7*	*46.5 (25.27)*	*21.42 (10.55)*	*8*	*48.9 (14.41)*	*16.14 (8.57)*	*5.28 [−26.30; 36.87]; 0.720*
EVOLVE-2	*26*	*53.0 (13.22)*	*25.74 (3.77)*	*21*	*48.3 (12.98)*	*13.79 (4.25)*	*11.95 [1.37; 22.53]; 0.028*
EVOLVE-1/-2[m]	33	51.7 (16.15)	23.99 (4.28)	29	48.4 (13.18)	14.06 (4.10)	9.93 [0.19; 19.67]; 0.046
REGAIN	30	40.4 (18.89)	20.07 (3.67)	96	38.1 (18.26)	12.01 (2.43)	8.07 [0.51 15.62]; 0.037
Total[f]							8.77 [2.80; 14.74]; 0.004 Hedges' g [95% CI][p]: 0.44 [0.14; 0.75]
Role Function-Preventive Domain							
EVOLVE-1	*7*	*60.0 (27.39)*	*8.72 (9.73)*	*8*	*68.5 (14.35)*	*15.28 (8.09)*	*−6.56 [−35.46; 22.35]; 0.630*
EVOLVE-2	*26*	*69.8 (15.09)*	*17.62 (3.68)*	*21*	*64.8 (15.41)*	*9.14 (4.23)*	*8.48 [−1.91; 18.87]; 0.107*
EVOLVE-1/-2[m]	33	67.8 (18.22)	14.74 (4.19)	29	65.8 (15.02)	9.01 (4.02)	5.74 [−3.76; 15.23]; 0.231
REGAIN	30	54.1 (21.48)	16.52 (3.47)	96	55.1 (21.08)	9.29 (2.29)	7.23 [0.05; 14.42]; 0.049
Total[f]							6.69 [0.96; 12.42]; 0.022 Hedges' g [95% CI][p]: 0.35 [0.05; 0.66]

Endpoint	Galcanezumab + BSC			Placebo + BSC			Galcanezumab + BSC vs placebo + BSC
	N[j]	Values at start of study[n] MV (SD)	Change[k] MV (SE)[l]	N[j]	Values at start of study[n] MV (SD)	Change[k] MV (SE)[l]	MD [95% CI]; p value[l]
MSQ[q]							
Emotional Function Domain							
EVOLVE-1	*7*	*50.5 (38.08)*	*20.38 (13.76)*	*8*	*54.7 (20.07)*	*14.27 (11.26)*	*6.11 [−34.91; 47.13]; 0.751*
EVOLVE-2	*26*	*69.6 (19.94)*	*15.12 (3.60)*	*21*	*62.7 (19.06)*	*12.83 (4.18)*	*2.29 [−7.96; 12.54]; 0.654*
EVOLVE-1/-2[m]	33	65.7 (25.27)	13.67 (4.66)	29	60.5 (19.40)	11.06 (4.48)	2.61 [−8.01; 13.23]; 0.624
REGAIN	30	45.9 (23.43)	22.94 (4.51)	96	44.9 (24.88)	10.37 (2.96)	12.57 [3.20; 21.95]; 0.009
Total[f]							8.21 [1.18; 15.24]; 0.022 Hedges' g [95% CI][p]: 0.35 [0.05; 0.66]

Side effects

Endpoint	Galcanezumab + BSC		Placebo + BSC		Galcanezumab + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
AEs (additionally shown)					
EVOLVE-1	*7*	*6 (85.7)*	*10*	*7 (70.0)*	-
EVOLVE-2	*27*	*23 (85.2)*	*28*	*21 (75.0)*	-
EVOLVE-1/-2[b]	34	29 (85.3)	38	28 (73.7)	-
REGAIN	36	25 (69.4)	110	58 (52.7)	-

Endpoint	Galcanezumab + BSC		Placebo + BSC		Galcanezumab + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
SAEs					
EVOLVE-1	*7*	*0 (0)*	*10*	*0 (0)*	-
EVOLVE-2	*27*	*0 (0)*	*28*	*1 (3.6)*	*0.34 [0.01; 8.76]; 0.510*
EVOLVE-1/-2[b]	34	0 (0)	38	1 (2.6)	0.36 [0.01; 9.20]; 0.533
REGAIN	36	1 (2.8)	110	0 (0)	5.64 [0.21; 153.10]; 0.302
Discontinuation because of AEs					
EVOLVE-1	*7*	*0 (0)*	*10*	*0 (0)*	-
EVOLVE-2	*27*	*0 (0)*	*28*	*0 (0)*	-
EVOLVE-1/-2[b]	34	0 (0)	38	0 (0)	-
REGAIN	36	0 (0)	110	1 (0.9)	0.54 [0.02; 14.70]; 0.713

a) RR, 95% CI, and p value: logistic regression with a term for treatment.
b) IPD meta-analysis; logistic regression with terms for treatment and study.
c) Mean proportion with 95% CI (per treatment group) and RR with 95% CI and p value (group comparison): grouped logit model for binomially distributed data with one term for treatment; replacement of missing values by LOCF.
d) Months 1–6 (EVOLVE-1/-2) or Months 1–3 (REGAIN).
e) IPD meta-analysis; grouped logit model for binomially distributed data with terms for treatment and study; replacement of missing values by LOCF.
f) Calculation by the IQWiG, meta-analysis with fixed effect.
g) No representation because not informative.
h) In the placebo + BSC arm, no person had an event at any time.
i) In the galcanezumab arm, no person had an event at any time; in the comparator arm, one patient had one event at one time-point (month 3).
j) Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
k) Migraine hours/month and PGI-I; averaged over Months 1–6 (EVOLVE-1/-2) or Months 1–3 (REGAIN); PGI-S and MSQ: averaged over Months 4–6 (EVOLVE-1/-2) or Month 3 (REGAIN).
l) MMRM with terms for treatment, geographical region, value at baseline and time (month) as well as for interactions treatment × time and value at baseline × time. For EVOLVE-1 and EVOLVE-2, beyond that (except for migraine hours/month) with a term for number of migraine days/month (< 8 / ≥ 8). For REGAIN, beyond that with terms for medication overuse and migraine prophylaxis during studies.
m) IPD meta-analysis; MMRM with terms for treatment, number of migraine days/month (< 8/ ≥ 8; no term for migraine hours/month), geographic region, value at start of study, time (month) and study, and for treatment interactions × time and value at start of treatment × time.
n) Migraine hours/month: Baseline phase; PGI-S and MSQ: value at start of treatment: PGI-I: no survey of the change at start of treatment.
o) Lower values mean a better health status, negative group differences mean an advantage for galcanezumab.
p) Calculation of the IQWiG

q) A higher score means a better health-related quality of life for the patient, positive group differences mean an advantage for galcanezumab.

Abbreviations used:
BSC: best supportive Care; IPD: individual patient data; CI: confidence interval; LOCF: Last Observation carried forward; MMRM: mixed model with repeated measurements; MD: mean difference; MSQ: Migraine-Specific Quality of Life Questionnaire; MV: mean value; n: Number of patients with (at least one) event; N: number of patients evaluated; n.c.: not calculable; PGI-I: Patient Global Impression of Improvement; PGI-S: Patient Global Impression of Severity; RCT: randomised controlled study; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event; vs: versus

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. 1,428,000–1,445,000 patients

b) Adult patients who are not responsive to or are unsuitable to 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 to 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 Emgality® (active ingredient: galcanezumab) at the following publicly accessible link (last access: 23 July 2019):

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

Treatment with galcanezumab 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:	
Galcanezumab	€ 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: 1 September 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.

b) Adult patients who are not responsive to or are unsuitable to 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:	
Galcanezumab	€ 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: 1 September 2019)

c) Adult patients who are not responsive to or are unsuitable to 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:	
Galcanezumab	€ 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: 1 September 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 19 September 2019.

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

Berlin, 19 September 2019

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

Prof Hecken