Justification

Gemeinsamer Bundesausschuss

to the Resolution 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

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient galcanezumab in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 April 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1 number 1 VerfO on 29 March 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2019 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of galcanezumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the

IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of galcanezumab.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of galcanezumab (Emgality®) in accordance with the product information

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

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[2] or Clostridium botulinum toxin type A[3]

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] General methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.
[2] 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.
[3] According to the marketing authorisation for chronic migraines.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In addition to galcanezumab, the active ingredient s amitriptyline, flunarizine, metoprolol, propranolol and topiramate, the antibodies erenumab and fremanezumab, and Clostridium botulinum toxin type A are approved for the prophylaxis of chronic migraine in the present therapeutic indication.

On 2. Within the framework of statutory health insurance, non-medicinal treatment within the patient group defined by the therapeutic indication is not considered an appropriate comparator therapy.

On 3. For the prophylaxis of migraine, the G-BA has passed a resolution on the benefit assessment of medicinal product with new active ingredients according to Section 35a SGB V for the antibody erenumab (resolution of 2 May 2019).

By resolution of 16 September 2010, valproic acid is prescribable for migraine prophylaxis in adulthood at the expense of the SHI (see Annex VI to Section K of the Pharmaceuticals Directive – prescribability of authorised medicinal products in non-approved therapeutic indications).

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication. In this regard, it should be noted that the reliable evidence on therapy options in the present therapeutic indication is limited overall and that no superiority of any of the active ingredients mentioned can be derived. Therefore, among the medicinal therapy options authorised in Germany, no active ingredient is to be explicitly emphasised as a therapy standard in migraine prophylaxis.

With erenumab and fremanezumab, two further medicinal products are approved in this therapeutic indication. Within the scope of the benefit assessment according to Section 35a SGB V, no additional benefit was found for erenumab in patient populations a) and b) compared with the appropriate comparator therapy. In patient population c), there is a hint for a considerable additional benefit compared with BSC. However, the resolution on the benefit assessment for fremanezumab is still pending. The significance of the antibodies can currently not be conclusively assessed because they have been on the market only a short time. The antibodies therefore do not represent the appropriate comparator therapy at the present time.

a) Patient population a) covers 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, taking into account the marketing authorisation and the previous therapy. For these patients, it would be appropriate to use or switch to one of these options: Metoprolol or propranolol or flunarizine or topiramate or amitriptyline. According to the marketing authorisation, flunarizine should only be used if treatment with beta receptor blockers is contraindicated or has not shown sufficient effect.
In the overall view, for u 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, metoprolol or propranolol or flunarizine or topiramate or amitriptyline are considered equally appropriate therapy alternatives, taking into account the marketing authorisation and the previous therapy.

b) In patient population b, the following options are available for 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: Valproic acid or Clostridium botulinum toxin type A. The “active ingredient class” here refers to a pharmacological active ingredient class. Thus propranolol and metoprolol as beta-blockers are to be subsumed under a class of active ingredients but not topiramate, flunarizine, or amitriptyline.
By resolution of 16 September 2010, valproic acid is prescribable for migraine prophylaxis in adulthood at the expense of the SHI (see Annex VI to Section K of the Pharmaceuticals Directive – prescribability of authorised medicinal products in non-approved therapeutic indications). Valproic acid is only to be used in adults with migraine, with or without aura, for whom migraine prophylaxis is indicated if a therapy with all other approved medicinal products was unsuccessful, had to be discontinued because of side effects, or could not be initiated because of contraindications. For chronic migraine, valproic acid should therefore only be considered if treatment with all other authorised medicinal product, including Clostridium botulinum toxin type A, was not successful or contraindicated.

Clostridium botulinum toxin type A is only authorised for patients with chronic migraine and is only suitable for a limited number of patients.

Overall, both valproic acid and Clostridium botulinum toxin type A are not regularly considered for all patients.

c) If patients were not responsive to or are unsuitable for or did not tolerate any of the aforementioned medicinal therapies/active ingredient classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid or Clostridium botulinum toxin type A), the indicated appropriate comparator therapy for this patient population c) is best supportive care (BSC). Overall, it is appropriate to consider BSC treatment alone only after all treatment options have been exhausted. Best supportive care is the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of galcanezumab is assessed as follows:

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.

For migraine prophylaxis in 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, the additional benefit for galcanezumab compared with the appropriate comparator therapy is not proven.

Justification:

For this patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of galcanezumab compared with the appropriate comparator therapy.

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.

For migraine prophylaxis in 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, the additional benefit for galcanezumab compared with the appropriate comparator therapy is not proven.

Justification:

For this patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of galcanezumab compared with the appropriate comparator therapy.

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).

For migraine prophylaxis in 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), there is a hint for a considerable additional benefit of galcanezumab compared with the appropriate comparator therapy best supportive care (BSC).

Justification:

The EVOLVE-1, EVOLVE-2, and REGAIN studies are used for the assessment of the additional benefit of galcanezumab in adult patients for whom only BSC therapy can be considered. The EVOLVE-1 and EVOLVE-2 studies investigated adults with episodic migraine; the REGAIN study investigated adults with chronic migraine.

EVOLVE-1 and EVOLVE-2 studies (episodic migraines)

The EVOLVE-1 and EVOLVE-2 studies are both randomised, double-blind pivotal studies comparing galcanezumab + BSC with placebo + BSC over a period of six months. Adult patients with at least 12 months of documented episodic migraine according to ICHD-3 (International Classification of Headache Disorders, 3rd Edition) were included. In addition, the patients must have had an average of 4–14 migraine days/month and ≥ 2 migraine attacks/month within the last three months. Adults with and without previous medicinal migraine prophylaxis were included. Patients who had failed 3 or more therapies of different active ingredient classes in appropriate doses were excluded from participation in the study. The following active ingredients were permitted as part of a previous medicinal therapy: the

anti-epileptics divalproex sodium, sodium valproate, and topiramate; the beta-blockers metoprolol, propranolol, timolol, atenolol, and nadolol; the antidepressants amitriptyline and venlafaxine; and botulinum toxin A or B. The triptans frovatriptan, naratriptan, and zolmitriptan were permitted exclusively for the prophylaxis of menstruation-associated migraine. An appropriate dosage was defined as the highest tolerated dose of an active ingredient for ≥ 2 months. A lack of response because of intolerance was not considered a therapy failure.

In total 862 patients in the EVOLVE-1 study and 922 patients in the EVOLVE-2 study were randomly assigned to treatment with galcanezumab (120 mg and 240 mg, respectively) or placebo at a ratio of 1:1:2. Of the patients who received at least one dose of the study medication, 213 (EVOLVE-1) and 231 (EVOLVE-2) were assigned to the relevant galcanezumab treatment arm (120 mg) and 433 (EVOLVE-1) and 461 (EVOLVE-2) were assigned to the placebo arm. The randomisation was stratified according to the migraine frequency determined in the baseline phase (< 8 migraine days/month vs ≥ 8 migraine days/month) as well as the geographical region. While the EVOLVE-1 study was conducted exclusively in the US, Canada, and Puerto Rico, the EVOLVE-2 study also had study centres in Europe.

Galcanezumab was administered subcutaneously in the relevant study arm according to the product information. The patients were also allowed to use medication for the acute treatment of a migraine attack.

The primary endpoint of the study was the change in the number of migraine days/month compared with baseline averaged over 6 months of double-blind treatment. Secondary endpoints were other endpoints of morbidity, quality of life, and adverse events (AEs).

REGAIN study (chronic migraine)

The REGAIN study is a randomised, double-blind pivotal studies comparing galcanezumab + BSC with placebo + BSC over a period of three months. Adult patients with chronic migraine according to ICHD-3 were included. Accordingly, chronic migraine is defined as headache on more than 15 days per month for a period of more than three months with the headache meeting the criteria for migraine on at least eight days. To be included in the study, patients must also have had ≥ 1 headache free calendar day per month within the last three months and during the baseline phase. Patients who received a stable dose of topiramate or propranolol for migraine prophylaxis ≥ 2 months before the start of the baseline phase were allowed to continue this treatment in parallel with the study medication. This concerned approximately 14% of the patients in the study. Also included were patients with medication-overuse headache in the baseline phase.

A total of 1,117 patients were randomly assigned to treatment with galcanezumab 120 mg (N = 279), galcanezumab 240 mg (N = 279), or placebo (N = 559) at a ratio of 1:1:2. Randomisation was stratified by country, overuse of acute headache medication determined in the baseline phase (yes vs no), and concomitant treatment with medication for migraine prophylaxis (yes vs no).

Galcanezumab was administered subcutaneously in the relevant study arm according to the product information. The patients were also allowed to use medication for the acute treatment of a migraine attack.

The primary endpoint of the study was the change in the number of migraine days/month compared with baseline averaged over 3 months of double-blind treatment. Secondary endpoints were other endpoints of morbidity, quality of life, and adverse events (AEs).

Relevant sub-population

The EVOLVE-1, EVOLVE-2, and REGAIN studies included both non-pretreated patients and patients with previous medication for migraine prophylaxis. Patients who had failed ≥ 3

therapies of different active ingredient classes in appropriate doses were excluded from participation in the study. A lack of response because of intolerance was not considered a therapy failure and was therefore not included in the number of previous therapies with therapy failure. There is no information available on the unsuitability of an active ingredient in the context of previous therapy.

For the benefit assessment, the pharmaceutical company submitted a sub-population of the EVOLVE-1, EVOLVE-2, and REGAIN studies. These sub-populations include patients who have been pretreated with at least two of the following therapies (active ingredient classes): propranolol/metoprolol, flunarizine, topiramate, or amitriptyline. The study sub-populations relevant for the benefit assessment include 17 patients from the EVOLVE-1 study, 55 patients from the EVOLVE-2 study, and 146 patients from the REGAIN study. Some of the patients in the relevant sub-populations were treated with valproic acid prior to inclusion in the study. (EVOLVE-1: 2 of 17 (11.8%); EVOLVE-2: 16 of 55 (29.1%); REGAIN: 44 of 146 (30.1%)). In accordance with the Pharmaceuticals Directive (Annex VI to Section K), valproic acid is only then prescribable for migraine prophylaxis in adults “if treatment with other authorised medicinal products has not been successful or is contraindicated”. Thus only those patients for whom the administration of valproic acid was the last therapy for medicinal migraine prophylaxis before the inclusion of the study would be relevant. However, this is not apparent from the data submitted.

In the treatment situation of migraine prophylaxis (especially with at least four migraine days per month at the time of therapy initiation), the various therapy options should ideally be considered. However, it cannot necessarily be assumed that the patients have not responded to all therapy options (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid, Clostridium botulinum toxin type A), are not suitable for them, or have not tolerated them before BSC comes into question.

In the context of a clinical study, treatment with BSC in patient group c) may be considered if the patients have previously been treated with at least two medicinal therapies or active ingredient classes (from the following: metoprolol, propranolol, flunarizine, topiramate, amitriptyline) or did not tolerate them.

Overall, the sub-populations presented in the EVOLVE-1, EVOLVE-2, and REGAIN studies can be regarded as a sufficient approximation of patient population c) and are therefore used for the benefit assessment. Nevertheless, the sub-populations of the studies used for the benefit assessment are subject to uncertainties as to whether they actually represent those patients for whom no further medicinal therapies can be considered and therefore best supportive care can be regarded as appropriate.

Guidelines and other scientific literature distinguish between episodic and chronic migraine in the indication area of migraine. However, based on the study data presented here, there is no indication that the effects of treatment differ in patients with episodic and chronic migraine. The results of the sub-populations with episodic and chronic migraine are therefore meta-analytically summarised in the present benefit assessment.

Implementation of the appropriate comparator therapy

Treatment with BSC includes both medicinal and non-medicinal treatment for the therapeutic indication migraine.

During treatment with the study medication, the use of acute medication was permitted in the EVOLVE-1, EVOLVE-2, and REGAIN studies for the treatment of migraine attacks: various analgesics (paracetamol, NSAIDs, triptans, ergotamine (derivatives), isometheptenes, dichloralphenazone-paracetamol combination preparations, other combinations of the aforementioned medications), antiemetics, opiates, or painkillers containing barbiturates (limited to a maximum of three applications per month) as well as a single steroid injection in an emergency. However, it should be noted that the list of permitted acute medication does not include all therapy options approved or recommended in Germany (e.g. metamizole). In

the two EVOLVE studies, the use of the triptans frovatriptan, naratriptan and zolmitriptan for the treatment of menstruation-associated migraine was also excluded.

In all three studies, in addition to acute medication, non-medicinal measures other than acupuncture, chiropractic, physiotherapy, and transcutaneous electrical nerve stimulation in the head and neck area were generally permitted. However, overall, no documented information is available on the non-medicinal therapies performed.

Despite the restrictions described and the resulting uncertainties in the EVOLVE-1, EVOLVE-2, and REGAIN studies, treatment in the placebo arm of the studies is considered to be an approximation to the appropriate comparator therapy BSC.

Extent and probability of the additional benefit

Mortality

No deaths occurred in the EVOLVE-1, EVOLVE-2, and REGAIN studies.

Morbidity

Symptomology (migraine days per month)

In the EVOLVE-1, EVOLVE-2, and REGAIN studies, a migraine day was defined as a calendar day on which a patient documented a migraine headache or a probable migraine headache. Migraine headache, in turn, was defined as headache with or without aura for ≥ 30 minutes, which also met the criteria of the ICHD-3 classification with regard to pain characteristics and accompanying symptomology.

For the endpoint symptomology (migraine days per month), responder analyses are used for a reduction of migraine days by ≥ 50%, ≥ 75% and 100% compared with the baseline phase, averaged over the treatment period.
In the endpoint “reduction of migraine days by ≥ 50%”, a statistically significant difference to the advantage of galcanezumab + BSC compared with placebo + BSC (RR 4.21 [95% CI 3.39; 5.24]; p value < 0.001) is shown in the meta-analysis.
In the endpoint “reduction of migraine days by ≥ 75%” there is heterogeneity between the results from the EVOLVE-1/-2 and REGAIN studies. A meta-analytical summary is therefore not useful. However, the results from the EVOLVE-1/-2 and the REGAIN studies showed a statistically significant advantage of galcanezumab + BSC compared with placebo + BSC.
In the endpoint “reduction of migraine days by 100%”, the meta-analytical consideration of the EVOLVE-1 and EVOLVE-2 studies shows a statistically significant advantage in favour of galcanezumab + BSC compared with placebo + BSC. In the REGAIN study, only one patient achieved a 100% reduction in migraine days per month during the treatment period (Month 3). A resulting effect estimate is therefore not informative.

In addition, the results of the operationalisation “migraine hours per month” are also presented (change compared with the baseline phase averaged over the treatment period). In the EVOLVE-1, EVOLVE-2, and REGAIN studies, the number of migraine hours per month was defined as the sum of headache hours within a 30-day period on days with migraine or probable migraine.

Both the EVOLVE-1/-2 meta-analysis and the REGAIN study showed a statistically significant advantage in favour of galcanezumab therapy. Because of the expected heterogeneity between the results from the EVOLVE-1/-2 and REGAIN studies, a further meta-analytical summary of the results for this operationalisation is not meaningful.

Headache days per month

In EVOLVE-1, EVOLVE-2, and REGAIN studies, a headache day was defined as a calendar day on which a patient documented any type of headache (migraine headache, probable migraine headache, non-migraine headache). For the benefit assessment, two additional operationalisations are used: Reduction of headache days by ≥ 50% compared with baseline averaged over treatment period and change in headache days per month compared with baseline. There are no evaluations of the reduction of headache days per month by ≥ 75% or by 100% compared with the baseline phase. In addition, analyses are only available for headache days as a whole but not differentiated according to migraine headache, probably headache, and non-migraine headache.

Both for the operationalisation "Reduction of headache days per month by ≥ 50%" (RR 3.63 [95% CI 2.87; 4.60]; p value < 0.001) and for the endpoint "Change in headache days per month" (RR −3.77 [95% CI −5.19; −2.34]; p value < 0.001) the meta-analytical summary shows a statistically significant advantage in favour of galcanezumab + BSC compared with placebo + BSC compared with the baseline phase.

Severity of the disease (PGI-S)

The Patient Global Impression of Severity (PGI-S) is a tool for assessing the severity of the disease. It consists of the question "How would you assess the severity of your condition if migraine were considered a chronic condition?" The assessment is made by the patient on a 7-step scale from "normal" to "extremely ill". In the EVOLVE-1, EVOLVE-2, and REGAIN studies, PGI-S was assessed monthly on the day of the first administration of the study medication as well as during the double-blind treatment phase.

For the disease severity (PGI-S) endpoint, the meta-analysis did not reveal any statistically significant difference between treatment groups.

Health status – Change of migraine condition during therapy (PGI-I)

The Patient Global Impression of Improvement (PGI-I) is a tool to measure the change in migraine condition compared with the beginning of the study medication. It consists of the item "Please select the response category that best describes your migraine condition since starting taking the study medication". The assessment is made by the patient on a 7-step scale from "much better" to "much worse". In the EVOLVE-1, EVOLVE-2 and REGAIN studies, PGI-I was assessed monthly during the double-blind treatment phase starting four weeks after first administration of the study medication.

For the endpoint change in migraine condition under therapy (PGI-I), the meta-analysis showed a statistically significant difference in favour of galcanezumab + BSC compared with placebo + BSC. The standardised mean difference (SMD) in the form of Hedges' g is used to assess the clinical relevance of the result. The 95% confidence interval is completely below the irrelevance threshold of −0.2. This is interpreted as a clinically relevant effect (Hedges' g −0.87 [95% CI −1.17; −0.57]).

<u>Quality of life</u>

In the EVOLVE-1, EVOLVE-2 and REGAIN studies, the health-related quality of life was assessed with the Migraine-Specific Quality of Life Questionnaire (MSQ), which measures the influence of migraine on health-related quality of life over the past four weeks and is composed of three domains: Role function restrictive domain (RFR; 7 items), role function preventive domain (RP; 4 items), and emotional function domain (EF; 3 items). The RFR domain questions the extent of migraine-related restrictions on everyday activities, work, family, and friends as well as concentration and energy. The RP domain provides information on the extent of migration-related restrictions with regard to participation in social activities,

everyday activities, and work. In the EF domain, the influence of migraine on the mental state of the patient is recorded. The values are determined using a Likert scale. A higher value corresponds to a higher health-related quality of life.
The pharmaceutical company presented responder analyses as part of the benefit assessment. However, because the validity of the response threshold values cannot be conclusively assessed because of contradictory information, the pre-specified mean value differences are used to assess the additional benefit for all three domains.

Based on the MSQ, the meta-analysis shows a statistically significant difference for all three domains in favour of galcanezumab + BSC compared with placebo + BSC. The standardised mean difference (SMD) in the form of Hedges' g is used to assess the clinical relevance of the results. Here the 95% confidence interval of the SMD for the three domains is not completely outside the irrelevance range of −0.2 to 0.2. Consequently, it cannot be concluded with sufficient certainty that the effects are clinically relevant in each case.

Side effects

SAEs and discontinuation because of AEs

While no SAEs occurred in the EVOLVE-1 study, a SAE in the placebo arm was observed in the EVOLVE-2 study, and a SAE in the galcanezumab arm was observed in the REGAIN study.
Discontinuation because of AEs did not occur in the EVOLVE-1 and EVOLVE-2 studies. In the REGAIN study, one patient in the placebo arm discontinued therapy because of AEs.
A meta-analytical summary of the results of EVOLVE-1/-2 and the REGAIN study is not required for these endpoints because of the very small number of events that occurred.
There is no higher or lower damage from galcanezumab + BSC compared with placebo + BSC for each of these endpoints.

Overall assessment/conclusion

For migraine prophylaxis in 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 from the EVOLVE-1 and EVOLVE-2 studies (episodic migraine) and the REGAIN study (chronic migraine) are available for galcanezumab. Based on the study data presented here, there is no indication that the effects of treatment differ in patients with episodic and chronic migraine. Therefore, in the present benefit assessment, the results are summarised meta-analytically whenever possible.

In the endpoint category morbidity, the endpoints "reduction of migraine days per month by ≥ 50%, ≥ 75%, and 100%" show statistically significant and to a large extent considerable advantages in favour of therapy with galcanezumab + BSC compared with placebo + BSC. This advantage is also reflected in the additional operationalisation "number of migraine hours per month compared to baseline". The reduction in the number of headache days per month also shows a statistically significant advantage in favour of treatment with galcanezumab. The endpoint "Change in migraine condition under therapy (PGI-I)" also shows a statistically significant and clinically relevant advantage of galcanezumab + BSC compared with placebo + BSC.

In the health-related quality of life endpoint category, the mean value differences used for all three domains of the MSQ show statistically significant differences in favour of galcanezumab + BSC compared with placebo + BSC. However, it cannot be concluded with sufficient certainty that the effects are clinically relevant in each case.

In the side effects category, no advantages or disadvantages can be deduced for galcanezumab compared with the appropriate comparator therapy BSC.
In the overall view, in the endpoint category morbidity, in three randomised, double-blind, and direct-comparative studies, there are only positive effects for galcanezumab compared with the appropriate comparator therapy. There are no negative results from other categories.

Based on these considerations, on the basis of the information in the dossier and the results of the benefit assessment, the G-BA considers the additional benefit for galcanezumab compared with the appropriate comparator therapy best supportive care for migraine prophylaxis in 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) to be a significant improvement of the therapy-relevant benefit not yet achieved and classifies the extent of the additional benefit as considerable.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on a randomised, double-blind, and direct comparison study. However, for the present benefit assessment of patient population c), only those patients who received 120 mg galcanezumab and were also pretreated with at least two of the following therapies (active ingredient classes) were relevant: Propranolol/metoprolol, flunarizine, topiramate, or amitriptyline.

There are still some uncertainties regarding the transferability of the study results to the German health care context. Based on the written statement procedure and taking into account the statements made by the medical societies, it cannot be assumed that in German health care situation patients are considered to be resistant to therapy or no longer treatable after only two previous therapies. Rather, these patients often receive further medicinal therapies for the prophylaxis of migraine. It therefore remains unclear to what extent the patients evaluated actually represent those patients for whom no further medicinal therapies can be considered and therefore best supportive care can be regarded as appropriate. It can therefore be assumed that at least some of the patients would have been considered for further therapy with at least one of the active ingredients mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid, Clostridium botulinum toxin type A). However, it is unclear how large this proportion is. However, there are uncertainties regarding the transferability of the study results to the everyday healthcare situation.

In the overall view, the reliability of data is classified as a hint.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Emgality® with the active ingredient galcanezumab.

The present assessment refers to the therapeutic indication “for prophylaxis of migraine in adults who have at least 4 migraine days per month”.

For the benefit assessment, the following patient groups were distinguished:

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

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

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).

Patient group a)

The G-BA determined metoprolol or propranolol or flunarizine or topiramate or amitriptyline as an appropriate comparator therapy, taking into account marketing authorisation and the previous therapy. The pharmaceutical company does not provide data for this patient group. In the overall view, for 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, the additional benefit for galcanezumab for migraine prophylaxis compared with the appropriate comparator therapy is not proven.

Patient group b)

Valproic acid[2] or Clostridium botulinum toxin type A[3] was determined as the appropriate comparator therapy by the G-BA. The pharmaceutical company does not provide data for this patient group. In the overall view, for 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, the additional benefit for galcanezumab for migraine prophylaxis compared with the appropriate comparator therapy is not proven.

Patient group c)

Best supportive care (BSC) was determined as an appropriate comparator therapy by the G-BA. For this patient group, the pharmaceutical company presents the results of a sub-population of the EVOLVE-1 and EVOLVE-2 studies (episodic migraine) as well as the REGAIN study (chronic migraine).

In the endpoint category morbidity, the endpoints “reduction of migraine days per month by ≥ 50%, ≥ 75%, and 100%” show statistically significant and to a large extent considerable advantages in favour of therapy with galcanezumab + BSC compared with placebo + BSC. This advantage is also reflected in the operationalisation “Number of migraine hours per month compared to baseline”, in the endpoint “Reduction of headache days per month”, and in the endpoint “Change of migraine condition during therapy (PGI-I)”.
In the endpoint category of health-related quality of life, there are statistically significant differences for all three domains of the MSQ in favour of galcanezumab + BSC compared with placebo + BSC. However, it cannot be concluded with sufficient certainty that the effects are clinically relevant in each case.

In the category of side effects, there are no differences between galcanezumab + BSC and placebo + BSC.

However, there are uncertainties as to what extent the patients evaluated actually represent those patients for whom no further medicinal therapies can be considered and therefore best supportive care can be regarded as appropriate. As a result, there are still some uncertainties regarding the transferability of the study results to the German health care context.

In the overall view, for 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), there is a hint for a considerable additional benefit of galcanezumab compared with the appropriate comparator therapy BSC.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI). These are mainly based on information provided by the pharmaceutical company in the dossier, the benefit assessment, and the IQWiG addendum of 3 September 2019. In the overall view, the number of patients per patient population is subject to uncertainties. The allocation of patient proportions to sub-populations a) through c) on the basis of routine data also leads to uncertainties. Furthermore, because of the methodology chosen to estimate the rate of increase for all patient groups, there are uncertainties with regard to the upper limits of the ranges shown. The data within the indication of migraine prophylaxis also differ significantly between the benefit assessments.

Based on the estimations of the IQWiG addendum of 3 September 2019 a range of approx. 1,428,000–1,445,000 patients was derived for patient group a in deviation from the resolution on erenumab of 2 May 2019 with additional consideration of the criterion “patients with < 4 migraine days per month”.

In contrast to the resolution on erenumab of 2 May 2019, the lower limit for patient group b) is the more plausible estimate of 1,400 patients because this takes into account the restriction to exactly the four active ingredient classes named by the G-BA. The upper limit, however, is the number of patients from the erenumab dossier (11,000 patients), which is considered more plausible. This is mainly due to the fact that in the dossier on galcanezumab, for the upper limit, the regulation was budgeted at only at least two (instead of four) prophylactics. Despite the fact that in the dossier on erenumab, patients with less than four migraine days per month were not also excluded for sub-populations b and c, based on the routine data analyses presented, it can be assumed that the patients in question were severely affected and regularly suffer from at least four migraine days per month; a more plausible approximation of the care reality was ultimately assumed. For patient group b), the overall range is thus 1,400 to 11,000 patients.

For patient group c), a range of approx. 14,000–15,000 patients is derived analogous to the resolution on erenumab of 2 May 2019. These figures are in line with the estimates of the IQWiG addendum of 3 September 2019.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2019).

It is assumed that one year will be used to calculate the costs for all medicinal products. This does not take into account the fact that treatment may be discontinued earlier because of non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients shall be taken into account in the application of the medicinal products.

In contrast to this, the costs for flunarizine are shown for 6 months because the product information limits the intake of flunarizine to a maximum of 6 months regardless of response. This does not prevent the resumption of flunarizine therapy at a later date. According to the product information, the initial dose of flunarizine is 5 mg once daily for patients over 65 years of age and 10 mg once daily for patients under 65 years of age. The initial dose should not be given longer than necessary to relieve symptoms (usually no longer than two months). For the maintenance dose, the daily dose should be reduced by taking flunarizine either only every second day or on five consecutive days followed by two non-treatment days. For the treatment costs of flunarizine, a range is shown taking the data into account; the lower limit of the span is the initial dose of 5 mg once a day followed by a maintenance dose every second day, while the upper limit of the span is 10 mg daily with a maintenance dose of five days of flunarizine followed by two non-treatment days. Treatment with flunarizine should be discontinued after 6 months at the latest and should only be resumed when the treated symptoms return. For the calculation only 6 months treatment duration are used. Nevertheless, the costs may be higher if a new treatment with flunarizine is started at a later date.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Galcanezumab	continuous, 1 × monthly	12	1	12
Best supportive care (patient population c)	no data available			
Appropriate comparator therapy				
Patient population a)				
Amitriptyline	continuous, 1 x daily	365	1	365
Flunarizine	up to 6 months	121–146	1	121–146
Metoprolol	continuous, 1 x daily	365	1	365
Propranolol	continuous, 2–3 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Topiramate	continuous, 2 x daily	365	1	365
Patient population b)				
Clostridium botulinum toxin type A[3]	continuously, every 12 weeks	4.3	1	4.3[4]
Valproic acid[2]	continuous	365	1	365
Patient population c)				
Best supportive care	no data available			

Usage and consumption:

In general, initial induction schemes are not taken into account for the cost representation because the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

Designation of the therapy	Dosage	Dose/patient /treatment days	Consumption by potency/treatme nt day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Galcanezumab	120 mg	120 mg	1 × 120 mg -	12	12 × 120 mg
Best supportive care (patient population c)	no data available				
Appropriate comparator therapy					
Patient population a)					
Amitriptyline	25 mg - 75 mg	25 mg - 75 mg	1 × 25 mg - 1 × 75 mg	365	365 × 25 mg - 365 × 75 mg
Flunarizine	5 mg - 10 mg	5 mg - 10 mg	1 × 5 mg - 1 × 10 mg	121 - 146	121 × 5 mg - 146 × 10 mg
Metoprolol	100 mg - 200 mg	100 mg - 200 mg	100 mg - 200 mg	365	365 × 100 mg - 365 × 200 mg
Propranolol	40 mg	80 mg - 120 mg	2 × 40 mg - 3 × 40 mg	365	730 × 40 mg - 1095 × 40 mg
Topiramate	50 mg	100 mg	2 × 50 mg	365	730 × 50 mg

[4] Data rounded here. The further calculation of the costs was carried out with non-rounded value.

Designation of the therapy	Dosage	Dose/patient /treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Patient population b)					
Clostridium botulinum toxin type A[3]	155–195 units	155–195 units	2 × 100 units	4.3[4]	8.6 × 100 units
Valproic acid[2]	500 mg[5] - 1500 mg	500 mg - 1500 mg	1 × 500 mg - 3 × 500 mg	365	365 × 500 mg - 1095 × 500 mg
Patient population c)					
Best supportive care	no data available				

Costs:

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates. If a fixed amount is available, this will be used as the basis for the cost calculation.

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Galcanezumab	3 SFI	€ 2,027.36	€ 1.77	€ 112.51	€ 1,913.08
Appropriate comparator therapy					
Patient population a)					
Amitriptyline 25 mg[6]	100 FCT	€ 18.27	€ 1.77	€ 0.58	€ 15.92
Amitriptyline 75 mg[6]	100 TAB	€ 31.62	€ 1.77	€ 1.63	€ 28.22
Flunarizine 5 mg[6]	100 HC	€ 32.49	€ 1.77	€ 1.70	€ 29.02
Flunarizine 5 mg[6]	50 HC	€ 22.36	€ 1.77	€ 0.90	€ 19.69
Flunarizine 10 mg[6]	100 HC	€ 52.32	€ 1.77	€ 3.27	€ 47.28

[5] Dosage according to: Annex VI to Section K of the Pharmaceuticals Directive Prescribability of authorised medicinal products in unauthorised therapeutic indications (off-label use) – V. valproic acid

[6] Fixed amount

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Flunarizine 10 mg[6]	50 HC	€ 33.07	€ 1.77	€ 1.75	€ 29.55
Metoprolol 100 mg[6]	100 TAB	€ 13.77	€ 1.77	€ 0.22	€ 11.78
Metoprolol 200 mg[6]	100 TAB	€ 19.17	€ 1.77	€ 0.65	€ 16.75
Propranolol[6]	100 TAB	€ 19.16	€ 1.77	€ 0.65	€ 16.74
Topiramate[6]	200 FCT	€ 83.34	€ 1.77	€ 5.72	€ 75.85
Patient population b)					
Clostridium botulinum toxin type A	3 × 100 units	€ 1,220.07	€ 1.77	€ 66.94	€ 1,151.36
Valproic acid 500 mg[6]	200 FCT	€ 44.80	€ 1.77	€ 2.67	€ 40.36
Abbreviations: FCT = film-coated tablets; HC = hard capsules; SFI = solution for injection; TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 September 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 6 March 2018.

On 29 March 2019, the pharmaceutical company submitted a dossier for the benefit assessment of galcanezumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 March 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient galcanezumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 March 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2019. The deadline for submitting written statements was 22 July 2019.

The oral hearing was held on 5 August 2019.

By letter dated 5 August 2019, the IQWiG was commissioned with a supplementary assessment of the data submitted. The addendum prepared by IQWiG was submitted to the G-BA on 21 August 2019.

By letter dated 27 August 2019, the IQWiG was commissioned with a supplementary assessment of the patient numbers. The addendum prepared by IQWiG was submitted to the G-BA on 3 September 2019.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 10 September 2019, and the proposed resolution was approved.

At its session on 19 September 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	6 March 2018	Determination of the appropriate comparator therapy
Working group Section 35a	30 July 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 August 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Subcommittee Medicinal product	27 August 2019	Commissioning of the IQWiG with the supplementary assessment of the patient numbers
Working group Section 35a	13 August 2019 20 August 2019 3 September 2019	Advice on the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG), evaluation of the written statement procedure
Subcommittee Medicinal product	10 September 2019	Concluding discussion of the proposed resolution

Plenum	19 September 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 19 September 2019

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

Prof Hecken