Justification

Gemeinsamer Bundesausschuss

to the Resolution 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

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 erenumab in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 November 2018. 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, number 1 VerfO on 29 October 2018.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 February 2019, 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 erenumab 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, and the statements submitted in the written statement and oral hearing procedure. 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 erenumab.

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 erenumab (Aimovig®) in accordance with product information

Aimovig is indicated for 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

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

a) 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

Valproic acid[2] or Clostridium botulinum toxin Type A[3]

b) 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)

Best supportive care

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] 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.

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 erenumab for the prophylaxis of migraine, the active ingredients metoprolol, propranolol, flunarizine, topiramate and amitriptyline, galcanezumab, and fremanezumab as well as Clostridium botulinum toxin type A are authorised 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. The G-BA has not passed any resolutions on the prophylaxis of migraine on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V. 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 galcanezumab and fremanezumab, two further medicinal products are approved in this therapeutic indication. While galcanezumab was only available on the German market for a few weeks at the time of the resolution, fremanezumab has not yet been placed on the market. Therefore, the therapeutic significance of these active ingredients cannot yet be assessed, and both active ingredients cannot be considered as appropriate comparator therapy.

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 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 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, 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 not suitable 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 erenumab 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 erenumab 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 erenumab 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 erenumab 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 erenumab 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 erenumab compared with the appropriate comparator therapy best supportive care (BSC).

Justification:

The LIBERTY study was submitted for the assessment of the additional benefit of erenumab in adult patients for whom only BSC therapy is available. The LIBERTY study is a randomised, double-blind, parallel group RCT designed to compare erenumab + BSC with placebo + BSC over 12 weeks in adult patients with episodic migraine documented for at least 12 months. Patients with an average of four to 14 migraine days per month (on average 9.1 migraine days per month) within the last 3 months and a therapy failure on two to four previous medicinal migraine prophylaxes were included. A total of 246 patients were randomly assigned to treatment with erenumab (N = 121) or placebo (N = 125). Patients received 140 mg subcutaneous erenumab or placebo every four weeks. The authorised standard dose of erenumab is only 70 mg. According to the product information, some patients may benefit from 140 mg. The dose used in the LIBERTY study is thus considered to be included in the marketing authorisation. In addition, the patients in both study arms received treatment with best supportive care.

The primary endpoint of the study was the proportion of patients with a ≥ 50% reduction in migraine days per month at week 12. Secondary endpoints were symptomology, other morbidity endpoints, quality of life, and adverse events (AEs).

The LIBERTY study predominantly included patients who had been pretreated with at least two of the following therapies/active ingredient classes: propranolol/metoprolol, flunarizine, topiramate, or amitriptyline. In addition, the pharmaceutical company included in the sub-population only those patients with prior treatment with valproic acid for whom valproic acid was the last therapy prior to inclusion in the study. This is because valproic acid is only prescribable according to Annex VI Section K of the Pharmaceuticals Directive if treatment with other authorised medicinal products has not been successful or is contraindicated. This operationalisation can be understood as a sufficient approximation to the requirements of the Pharmaceuticals Directive.

The relevant sub-population of the LIBERTY study for the present benefit assessment comprises a total of 193 randomised patients (erenumab + BSC, N = 88, and Placebo + BSC, N = 105).

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-population presented in the LIBERTY study can be regarded as a sufficient approximation of patient population c and is therefore used for the benefit assessment. According to ICHD-3, chronic migraine is defined as headache on more than 15 days per month for a period of more than three months with headache fulfilling the criteria for migraine on at least eight days. On the other hand, episodic migraine is defined as up to 14 migraine days per month. Patients in the relevant sub-population of the LIBERTY study, who had an average of 8.5 migraine days, were in a transition between episodic and chronic migraine; to baseline, 71% of patients had 8–14 migraine days a month. Migraine is also a continuum between episodic and chronic manifestations in which patients can change between both forms in phases. Furthermore, the sub-group analyses presented showed no interaction by migraine days per month (4 to 7 vs 8 to 14). Thus, a distinction between episodic and chronic migraine is not considered necessary.

Extent and probability of the additional benefit

Mortality

Overall mortality

In the LIBERTY study, no death occurred in either of the two study arms. For the endpoint overall mortality, there was no statistically significant difference between the treatment groups.

Morbidity

Symptomology (migraine days per month; migraine attacks per month)

In the LIBERTY study, a migraine day was defined as a calendar day on which a patient documented migraine headache. Migraine headache, in turn, was defined as migraine with

or without aura for at least 30 minutes. This also met the criteria of the ICHD-3 classification for pain intensity and/or acute medication. Pain is considered patient-relevant.

For the endpoint migraine days per month, evaluations for the (pre-specified) mean change in the number of migraine days per month at week 12 and responder analyses with the (pre-specified) response criteria of a reduction in migraine days per month by ≥ 50%, ≥ 75%, and 100% at the end of the double-blind treatment (in each case compared to the baseline phase) were presented. For the endpoint migraine days per month, the responder analyses for a reduction of ≥ 50% are used. A statistically significant difference to the advantage of erenumab + BSC compared with placebo+ BSC can be deduced: in the LIBERTY study, under erenumab + BSC, 30% of patients (26 out of 86) achieved a reduction of migraine days per month by ≥ 50% , under placebo + BSC, this was achieved by only 14% of patients (14 out of 104) (RR: 2.25 [95% CI: 1.25; 4.03]; p= 0.005). This advantage is considered to be considerable.

The pre-specified responder analyses for the endpoint “migraine attacks per month” are also presented. In the LIBERTY study, a migraine attack was operationalised as an episode of qualified migraine headache or taking migraine-specific acute medication as part of an aura. The statistically significant advantage in favour of erenumab + BSC is also shown in the endpoint “migraine attacks per month”; in the LIBERTY study 23% of patients (20 out of 86) treated with erenumab + BSC achieved a reduction of ≥ 50% migraine attacks per month, whereas under placebo + BSC, 12% of patients (12 out of 104) achieved this event (RR: 2.02 [95% CI: 1.05; 3.88]; p= 0.033).

Health status (EQ-5D VAS)

In the LIBERTY study, health status was reported by patients using the visual analogue scale of the EQ-5D-5L with which patients answered the question about their health status at the time of the measurement. 0 stands for the worst imaginable health status and 100 for the best imaginable health status. The VAS of EQ-5D-5L is included in the morbidity category for the benefit assessment. For the mean change of VAS to week 12 compared with baseline, the LIBERTY study showed no statistically significant advantage or disadvantage for erenumab + BSC compared with placebo + BSC.

Physical function (MPFID)

The patient diary *“Migraine Physical Function Impact Diary (MPFID)”* is a tool for measuring physical functioning. This includes the two domains “effects on daily activities” (7 items) and “physical impairment” (5 items) as well as an item for assessing the “overall effect of migraine on daily activities”. The values are collected using a Likert scale; each item can have values between 1 and 5. The degree of physical function is classified by item; the point values per item are added up within the domain and transformed to 0 to 100. Separate scores are created for each of the two domains and the superordinate question. A higher value corresponds to a pronounced impairment of physical functioning by migraine.

For the three scores “Effects on daily activities”, “Physical impairment”, and “Total effect on daily activities”, evaluations of the mean change at week 12 compared with baseline were presented in the dossier; these are taken into account for the present benefit assessment. For the endpoint physical function, a statistically significant effect to the advantage of erenumab + BSC is observed for each of the three domains for the mean change. Neither standardised irrelevance thresholds for group differences nor intra-individual responder analyses for a validated response criterion were presented. Standardised mean differences (SMD) in the form of standardised mean differences according to Hedges’ g are therefore used. Because the 95% confidence interval (CI) of the standardised mean value differences

(SMD) in the form of Hedges' g is not completely outside the irrelevance range of −0.2 to 0.2 in any of the three domains of the MPFID, it cannot be deduced that the effects are clinically relevant in each case.

Work productivity and activity impairment (WPAI headache)

The *Work Productivity and Activity Impairment (WPAI-Headache)* is a tool to measure the impairment of labour productivity and activities within the last seven days. The questionnaire consists of six questions covering total work productivity and daily activity restriction and can be adapted to a specific disease. On the basis of the questions, scores indicating the percentage of headache impairment are calculated: absence from work resulting from impairment because of headache (absenteeism), impairment because of headache at work (presenteeism), impairment of work because of headache (absenteeism + presenteeism), and impairment of daily activities because of headache. The evaluations of absenteeism, presenteeism, and impairment of work because of headache only include values from patients who were employed at the start of study.

For the benefit assessment, the evaluations for the mean change at week 12 compared with baseline are taken into account because neither standardised irrelevance thresholds for group differences nor intra-individual responder analyses were presented. For the endpoint work productivity and activity impairment measured by WPAI headache, there is no statistically significant difference between treatment groups for the "absenteeism" score. For the score "Activity impairment", on the other hand, a statistically significant, clinically relevant effect in favour of erenumab + BSC compared to placebo + BSC can be observed, taking into account the standardised mean difference in the form of Hedges' g (MD: −7.74 [95% CI: −14.55; −0.93]; p = 0.026; Hedges' g: −0.32 [−0.47; −0.22]). Furthermore, for the scores "Presenteeism" and "Total restriction (absenteeism + presenteeism)", there is a statistically significant advantage for erenumab + BSC compared with placebo + BSC. However, because the 95% CI of the standardised mean differences for the last mentioned scores "Presenteeism" and "Total restriction (absenteeism + presenteeism)" are not completely outside the irrelevance range of −0.2 to 0.2, it cannot be deduced for these scores that these effects are clinically relevant in each case.

Health-related quality of life

General impairment because of headache (HIT-6) – Improvement by ≥ 5 points

In the LIBERTY study, health-related quality of life was measured using the Headache Impact Test-6 (HIT-6). This is a tool used to assess a patient's impairment associated with headache within the past month. The severity of the impairment because of headache is determined using a Likert scale; depending on the answer, the questions are weighted (with 6, 8, 10, 11 or 13 points) and a total score is formed. This can have values between 36 and 78. Higher values correspond to a more pronounced impairment by headache.

In the dossier, the pharmaceutical company presented analyses of the mean change at week 12 as well as of the proportion of patients with an improvement and deterioration in the overall HIT-6 score by ≥ 5 points each. Because of the therapeutic objective of migraine prophylaxis, the present assessment focuses on improving the impairment caused by headache so that for HIT-6, the improvement by ≥ 5 points is included in the present benefit assessment on the basis of the pre-specified threshold value. There is a statistically significant advantage for erenumab + BSC compared with placebo + BSC; significantly more patients achieve an improvement of ≥ 5 points in HIT-6 under erenumab + BSC (51%)

compared with treatment with placebo + BSC (27%) (RR: 1.90 [95% CI: 1.30; 2.77]; p< 0.001). This advantage is considered to be considerable.

Side effects

SAEs and discontinuation because of AEs

For the endpoints SAEs and discontinuation because of AEs, there was no statistically significant difference between the treatment groups erenumab + BSC and placebo + BSC at week 12.

Overall assessment

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), the results of the LIBERTY study at week 12 are available for the assessment of erenumab.

In summary, the endpoint categories morbidity for the endpoint “migraine days per month” and health-related quality of life at week 12 show statistically significant, considerable benefits for erenumab + BSC compared with placebo + BSC. For the endpoint “activity impairment” (WPAI), there is a non-quantifiable, statistically significant, clinically relevant advantage for erenumab + BSC compared with placebo + BSC.

In the side effects category, at week 12, no advantages or disadvantages can be deduced for erenumab compared with the appropriate comparator therapy BSC.

In the overall view, in the endpoint categories of morbidity and health-related quality of life, the effects of erenumab compared with the appropriate comparator therapy in the study at week 12 are exclusively positive. These are not matched by 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 erenumab 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 additional benefit is assessed on the basis of the randomized, double-blind Phase III LIBERTY study. From this study, the part of the patients included that met the characteristics of the patient population c because of previous therapies was relevant for the benefit assessment.

For the LIBERTY study presented, the risk of bias is classified as low at study level. While the risk of bias at the endpoint level for the endpoints overall mortality, general impairment by headache (HIT-6), and health status (EQ-5D VAS) as well as serious AEs (SAEs) and discontinuation because of AEs is considered low, this is considered high for the endpoints symptomology (migraine days per month), physical function (MPFID), and work productivity and activity impairment (WPAI headache). For the endpoints with a high risk of bias, it is unclear whether a significant number of days or significant time periods were disregarded during the observation phase.

There are still some uncertainties regarding the transferability of the study results to the German health care context. Based on the written and oral 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 to four previous therapies. Rather, 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 best supportive care can be regarded as appropriate against the background of their burden of disease.

Further uncertainties arise from the fact that the study does not provide a clear demarcation between episodic and chronic migraine. While the study was actually designed to investigate patients with episodic migraine, based on the migraine days at the start of study, it can be assumed that patients with chronic migraine were also included. It is not possible to determine how high this proportion actually was because important information on categorisation was not provided. Furthermore, it remains unclear whether the results from the study are applicable to all patients with chronic migraine (defined according to ICHD-3) for whom only treatment with BSC can be considered.

In the overall view, the reliability of data provides a hint for an additional benefit.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Aimovig® with the active ingredient erenumab.

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)

<u>Patient group a</u>

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 erenumab for migraine prophylaxis compared with the appropriate comparator therapy is not proven.

Patient group b

Valproic acid[4] or Clostridium botulinum toxin type A[5] 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 erenumab 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 the RCT LIBERTY at week 12. This allows comparative statements for erenumab + BSC compared with placebo + BSC.

At week 12, in the morbidity category for the endpoint “migraine days per month”, a statistically significant, considerable advantage can be derived for erenumab + BSC compared with placebo + BSC. Within morbidity, a statistically significant, clinically relevant effect in favour of erenumab + BSC versus placebo + BSC was observed for the endpoint “activity impairment” (WPAI).

In the health-related quality of life category, there is a statistically significant, considerable advantage for erenumab + BSC compared with placebo + BSC at week 12, whereas in the adverse events category, there are no differences between erenumab + BSC and placebo + BSC at week 12.

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 erenumab 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). The resolution will be based on the information from the dossier of the pharmaceutical company. In the overall view, these are subject to uncertainties per patient population. For sub-population a, for example, there is a tendency to overestimate because patients with < 4 migraine days per month were not excluded; this limitation also applies to the sub-populations b and c. The allocation of patient proportions to sub-populations a to 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.

[4] 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.
[5] According to the marketing authorisation for chronic migraines.

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 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.

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: 15 April 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				
Erenumab	continuously, every 4 weeks	13	1	13
Best supportive	no data available			

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
care (patient population c)				
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
Topiramate	continuous, 2 x daily	365	1	365
Patient population b)				
Clostridium botulinum toxin type A[6]	continuously, every 12 weeks	4.3	1	4.3[7]
Valproic acid[8]	continuous	365	1	365
Patient population c)				
Best supportive care	no data available			

Usage and consumption:

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
Medicinal product to be assessed					
Erenumab	70 mg -	70 mg -	1 × 70 mg -	13	13 × 70 mg -
	140 mg	140 mg	2 x 70 mg		26 × 70 mg -
Best supportive care (patient population c)	no data available				
Appropriate comparator therapy					
Patient population a)					
Amitriptyline	25 mg -	25 mg -	1 × 25 mg -	365	365 × 25 mg -

[6] According to the marketing authorisation for chronic migraines.
[7] Data rounded here. The further calculation of the costs was carried out with non-rounded value.
[8] 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.

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
	75 mg	75 mg	1 × 75 mg		365 × 75 mg
Flunarizine	5 mg -	5 mg -	1 × 5 mg -	121 -	121 × 5 mg -
	10 mg	10 mg	1 × 10 mg	146	146 × 10 mg
Metoprolol	100 mg -	100 mg -	100 mg -	365	365 × 100 mg -
	200 mg	200 mg	200 mg		365 × 200 mg
Propranolol	40 mg	80 mg -	2 × 40 mg -	365	730 × 40 mg
		120 mg	3 × 40 mg		1095 × 40 mg
Topiramate	50 mg	100 mg	2 × 50 mg	365	730 × 50 mg
Patient population b)					
Clostridium botulinum toxin type A[9]	155–195 units	155–195 units	2 × 100 units	4.3[7]	8.6 × 100 units
Valproic acid[8]	500 mg[10] -	500 mg -	1 × 500 mg -	365	365 × 500 mg -
	1500 mg	1500 mg	3 × 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.

[9] According to the marketing authorisation for chronic migraines.
[10] Dosage according to: Annex VI to Section K of the Pharmaceuticals Directive Prescribability of authorised medicinal products in unauthorised therapeutic indications (off-label use) – Valproic acid

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Erenumab	3 PEN	€ 2,027.36	€ 1.77	€ 112.51	€ 1,913.08
Appropriate comparator therapy					
Patient population a)					
Amitriptyline 25 mg[11]	100 FCT	€ 18.27	€ 1.77	€ 0.58	€ 15.92
Amitriptyline 75 mg[11]	100 TAB	€ 31.62	€ 1.77	€ 1.63	€ 28.22
Flunarizine 5 mg[11]	100 HC	€ 32.49	€ 1.77	€ 1.70	€ 29.02
Flunarizine 5 mg[11]	50 HC	€ 22.36	€ 1.77	€ 0.90	€ 19.69
Flunarizine 10 mg[11]	100 HC	€ 52.32	€ 1.77	€ 3.27	€ 47.28
Flunarizine 10 mg[11]	50 HC	€ 33.07	€ 1.77	€ 1.75	€ 29.55
Metoprolol 100 mg[11]	100 TAB	€ 13.77	€ 1.77	€ 0.22	€ 11.78
Metoprolol 200 mg[11]	100 TAB	€ 19.17	€ 1.77	€ 0.65	€ 16.75
Propranolol[11]	100 TAB	€ 19.16	€ 1.77	€ 0.65	€ 16.74
Topiramate[11]	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[11]	200 FCT	€ 44.80	€ 1.77	€ 2.67	€ 40.36
Abbreviations: PEN = prefabricated pen; FCT = film-coated tablets, HC = hard capsules, TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 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.

[11] Fixed amount

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

In a letter dated 21 July 2017, the pharmaceutical company requested consultation in accordance with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) on, among other things, the question of appropriate comparator therapy. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 September 2017. The consultation meeting took place on 28 September 2017.

At the time of the consultation, the appropriate comparator therapy established by the G-BA was reviewed on the basis of the planned therapeutic indication. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 7 November 2017.

On 29 October 2018, the pharmaceutical company submitted a dossier for the benefit assessment of erenumab to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

By letter dated 29 October 2018 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 erenumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 January 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 February 2019. The deadline for submitting written statements was 22 February 2019.

The oral hearing was held on 11 March 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 24 April 2019, and the proposed resolution was approved.

At its session on 2 May 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 September 2017	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	7 November 2017	Change of the appropriate comparator therapy
Working group Section 35a	6 March 2019	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal product	11 March 2019	Conduct of the oral hearing
Working group Section 35a	20 March 2019 3 April 2019 17 April 2019	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure
Subcommittee Medicinal product	24 April 2019	Concluding discussion of the proposed resolution
Plenum	2 May 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 May 2019

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

Prof Hecken