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 Fremanezumab

of 7 November 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 fremanezumab in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 May 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 14 May 2019.

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 15 August 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 fremanezumab 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 fremanezumab.

In the light of the above and taking into account the statements 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 fremanezumab (Ajovy®) in accordance with product information

AJOVY® 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, 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 fremanezumab, the active ingredients amitriptyline, flunarizine, metoprolol, propranolol and topiramate, the antibodies erenumab and galcanezumab, and Clostridium botulinum toxin type A are approved for 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 passed two resolutions on migraine prophylaxis on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V for erenumab (resolution dated 2 May 2019) and for galcanezumab (resolution dated 19 September 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.

Patient population a) covers untreated adult patients and patients who have responded inadequately or are unable to tolerate 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 consideration of the combined evidence presented, for untreated adult patients who have responded inadequately, 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.

In patient population b), the following options are available for patients who are not responsive to 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.

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

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.
Annex VI of Section K of the AM-RL is currently being revised[4]. Thereafter, valproic acid will continue to be employed only if treatment with all other approved medicinal products has not been successful. The newly approved antibodies should also be considered before valproic acid is administered. These have not yet been established in healthcare provision owing to their recent market availability, and they have, therefore, not yet been assessed as part of the appropriate comparative therapy.

Overall, both valproic acid and Clostridium botulinum toxin type A are not regularly considered for all patients, but instead represent treatment options for particular patients.
If patients were not responsive to 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.

[4] See resolution of 6 August 2019 on the initiation of a written statement procedure on the amendment of the Pharmaceuticals Directive: Annex VI - valproic acid for migraine prophylaxis in adults

With erenumab and galcanezumab, 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 either for erenumab or galcanezumab 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 for both erenumab and galcanezumab. The significance of the antibodies cannot currently be conclusively assessed because they have been on the market only a short time, and the antibodies have not yet been established in healthcare provision. The antibodies therefore do not represent the appropriate comparator therapy at the present time.

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

2.1.1 Extent and probability of the additional benefit

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

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

For migraine prophylaxis in untreated adult patients who have responded inadequately or are unable to tolerate at least one prophylactic medication, the additional benefit for fremanezumab 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 fremanezumab compared with the appropriate comparator therapy.

Irrespective of the analyses presented for sub-population a), the two pivotal studies HALO CM and HALO EM submitted by the pharmaceutical company are not suitable for assessing the additional benefit of fremanezumab in comparison with the appropriate comparator therapy. Both the continuation of an existing inadequate therapy, as performed in the comparator arm of both studies, and the administration of placebo alone cannot be considered to be equivalent to implementing an 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 fremanezumab 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 fremanezumab 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 fremanezumab compared with the appropriate comparator therapy best supportive care (BSC).

Justification:

The FOCUS trial was submitted for the assessment of the additional benefit of fremanezumab in adult patients for whom only BSC therapy is available. The FOCUS trial is a randomised, multi-centric, double-blind, parallel group RCT designed to compare fremanezumab with placebo, double-blinded over 12 weeks, in adult patients with chronic or episodic migraine documented for at least 12 months. The 12-week double-blind phase was followed by a 12-week open study phase in which all patients received fremanezumab. The study included a total of 838 patients with episodic migraines (EM) or chronic migraines (CM) for whom treatment failed in 2 to 4 different migraine prophylaxis drug classes over the last 10 years. To be included in the study, EM patients needed to have had a mean of ≥ 6 and < 15 headache days in the run-in phase, including at least ≥ 4 migraine days. Patients with CM needed to have experienced a mean of ≥ 15 headache days within the run-in phase, of which ≥ 8 were migraine days. Patients received monthly or quarterly fremanezumab (in different treatment arms) or placebo. In all study arms during the study, subjects were permitted to take acute medication for acute migraine attacks if required. A total of 838 patients were randomly assigned 1:1:1 to treatment with monthly fremanezumab (N = 283; dosing regimen different for EM and CM), quarterly fremanezumab (N = 276; same dosing regimen for EM and CM) or placebo (N = 279).

Patients in the study receiving a quarterly fremanezumab dose all received 675 mg of fremanezumab. Patients receiving the monthly dose had different dosing schemes depending on whether they suffered from EM or CM. Patients with EM received a total of 3 doses of 225 mg of fremanezumab per month. In contrast, patients with CM received one initial dose of 675 mg of fremanezumab followed by 2 additional 225 mg doses per month. The dose of fremanezumab administered in the study (225 mg monthly or 675 mg quarterly) for patients with EM was compliant with the marketing authorisation detailed in the product information. For all patients, the product information specifies either a monthly dose of 225 mg or a quarterly dose of 675 mg of fremanezumab, regardless of whether they suffer from episodic or chronic migraine. The fremanezumab dosing scheme for CM patients in the study (initial dose of 675 mg followed by 2 further 225 mg doses) differs from that specified in the product information. According to the EMA, the 2 dosing schemes (with and without an initial dose of 675 mg for chronic migraine patients) are comparable in the present indication. The present benefit assessment considers the dosing scheme used in the study to be appropriate.

The study's primary endpoint was the mean change in average monthly migraine days versus baseline. Secondary endpoints were other endpoints of morbidity, quality of life, and adverse events (AEs).

The FOCUS trial predominantly included patients for whom treatment with at least 2 of the following previous therapies/active ingredient classes had been documented to have failed: beta-blockers (metoprolol, propranolol, atenolol, bisoprolol), anticonvulsants (topiramate), tricyclic antidepressants (amitriptyline), calcium channel blockers (flunarizine), angiotensin II antagonists (candesartan), Clostridium botulinum toxin type A and valproic acid. Therapy failure was considered to have occurred if no clinically significant improvement had occurred after at least 3 months of stable dose migraine prophylaxis therapy, if treatment had to be discontinued due to an adverse event, or if treatment was contraindicated or unsuitable for prophylactic migraine treatment of the patient.

The relevant sub-population of the FOCUS trial for the present benefit assessment comprises a total of 583 randomised patients (fremanezumab N = 388 and placebo N = 195).

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 not responded to or do not tolerate at least two medicinal therapies or active ingredient classes (from the following: metoprolol, propranolol, flunarizine, topiramate, amitriptyline).

Treatment with BSC includes both medicinal and non-medicinal treatment for the therapeutic indication migraine. Non-medicinal treatments were not explicitly mentioned in the study. In addition, no documented information is available on the non-medicinal therapies provided. Nevertheless, in the FOCUS trial patients were permitted to take acute medication for acute migraine attacks if required; this was documented individually for each patient in an electronic patient diary. As both acute and non-medicinal therapies were permitted, the placebo arm of the study is considered to be a sufficient approximation to BSC appropriate comparator therapy.

Overall, the presented sub-population from the FOCUS trial can be regarded as a sufficient approximation of patient population c) and is therefore used for the benefit assessment.

<u>Extent and probability of the additional benefit</u>

Mortality

Overall mortality

No mortalities were reported in the two study arms of the FOCUS trial. For the endpoint overall mortality, there was no statistically significant difference between the treatment groups.

Morbidity

Symptomatology (migraine days per month)

For the FOCUS trial, a migraine day was considered to be either a calendar day on which a patient documented a migraine headache or a probable migraine headache or to be a day in which the patient used migraine-specific headache medication (triptan or ergot derivatives).

A migraine headache, in turn, was defined as headache with or without aura for four consecutive hours, which also met the criteria of the ICHD-3 classification with regard to pain characteristics and accompanying symptomatology.

For the symptomatology endpoint (migraine days per month), responder analyses are used to record decreases in migraine days of ≥ 50%, ≥ 75% and 100% compared with the baseline phase, averaged over the treatment period.

With regards to a decrease in migraine days/month of ≥ 50 % compared to the baseline phase, as a mean over the period of treatment, a statistically significant advantage in favour of fremanezumab + BSC was shown over placebo + BSC. With regards to a decrease in migraine days/month of ≥ 75 % compared to the baseline phase, as a mean over the period of treatment, a statistically significant difference in favour of fremanezumab + BSC was also shown compared to placebo + BSC. As a mean over the treatment period, no statistically significant difference in 100% decrease in migraine days/month compared to baseline could be demonstrated between fremanezumab + BSC and placebo + BSC.

Headache days per month

In the FOCUS trial, a headache day was defined as a calendar day on which a patient experienced ≥ 4 consecutive hours of headache of any severity. Days in which patients experienced headaches of any severity and duration that required the use of migraine-specific acute medication (triptan or ergot derivatives) were also documented as headache days. The benefit assessment also draws on the operationalisation "change in headache days per month" compared to baseline phase, as a mean over the treatment period. There are no evaluations of the decrease in headache days per month of ≥ 50%, ≥ 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.

With regards to the endpoint “mean change in headache days per month” compared to the baseline phase, as a mean over the period of treatment of 12 weeks, a statistically significant advantage in favour of fremanezumab + BSC was shown over placebo + BSC.

Health status (EQ-5D VAS)

In the FOCUS trial, health status was reported by patients using the EQ-5D-5L visual analogue scale, which patients used to report on their health status at the time of the measurement. 0 indicates 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 FOCUS trial showed a statistically significant advantage for fremanezumab + BSC compared with placebo + BSC. To assess the clinical relevance of the findings the study calculated an SMD as a Hedges' g. The 95 % confidence interval of the SMD was 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.

Work productivity and activity impairment (WPAI headache)

The Work Productivity and Activity Impairment (WPAI) headache questionnaire tool primarily records health-related reductions in productivity while at work and in daily activities over the last 7 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.

The benefit assessment does not draw on the analyses for absenteeism and presenteeism from the WPAI headache questionnaire. The G-BA reassessed the importance of the endpoint for early benefit assessment, as the WPAI questionnaire predominantly records health-related productivity impairment factors. Absenteeism and presenteeism can no longer be considered to be suitable factors in the benefit assessment, nor in the context of IQWiG's underlying dossier on which the assessment is based. Impairment of daily activities due to headache (question 6) addresses a patient-relevant factor. However, this factor is not presented in this benefit assessment, as it is adequately accounted for in the HIT-6 tool.

Health-related quality of life

General impairment due to headache (HIT-6)
In the FOCUS trial, general impairment was measured using the Headache Impact Test-6 (HIT-6) tool. This is 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 deterioration of general impairment due to headache.

The general impairment due to headache (HIT-6) endpoint is based on mean differences. There is a statistically significant difference at week 12 compared to baseline in favour of fremanezumab + BSC over placebo + BSC. The standardised mean difference (SMD) in the form of Hedges' g is used to assess the clinical relevance of the results. The 95 % confidence interval of the SMD was completely outside the irrelevance range of −0.2 to 0.2. This is interpreted as a clinically relevant effect.

Migraine-Specific Quality of Life (MSQoL) questionnaire

In the and FOCUS trial health-related quality of life was assessed by means of the Migraine-Specific Quality of Life (MSQoL) questionnaire, which scores the influence of migraine on health-related quality of life over the past four weeks and is composed of three domains: a role function-restrictive (RFR) domain with 7 items, a role function-preventive (RP) domain with 4 items, and an emotional function (EF) domain with 3 items. The RFR domain documents the extent of migraine-related restrictions on everyday activities, work, family, and friends as well as on 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 an improved health-related quality of life.
The pharmaceutical company presented responder analyses as part of the benefit assessment. However, as the response threshold values were not pre-specified, the benefit assessment is based on the pre-specified mean differences for all three domains.

The endpoint employs the mean differences, each in conjunction with Hedges' g SMD values. Between week 12 and baseline for all three MSQoL domains (role function-restrictive, role function-preventive and emotional function), a statistically significant benefit has been demonstrated for fremanezumab + BSC over placebo + BSC. The 95 % confidence intervals of the SMDs for the role function-restrictive and emotional function domains were both completely outside the irrelevance range of −0.2 to 0.2. The 95 % confidence interval of the SMD for the role function-preventive domain was not completely outside the irrelevance range of −0.2 to 0.2. Accordingly, the MSQoL role function-preventive domain is inadequate to determine whether the effects at week 12 are clinically relevant, whereas the other two MSQoL domains (role function-restrictive and emotional function) are both statistically significant and clinically relevant at week 12.

Side effects

SAEs and discontinuation because of AEs

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

Specific AEs

Specific AEs for the benefit assessment were selected, on the one hand, from events in the relevant study, based on the frequency and differences between treatment arms and taking into account the relevance to patients. On the other hand, specific AEs were also selected if these were considered to be particularly important factors in the clinical presentation or for the active ingredients employed in the study.

The documentation submitted by the pharmaceutical company only included data on AEs for the relevant sub-population at system organ class (SOC) level. Information on preferred terms (PT) were not submitted. Selection of specific AEs based on the data submitted is not possible. The documentation assumes that the results on specific AEs do not call into question the findings on side effects nor the overall assessment of additional benefit. Overall, there are no statistically significant differences in the overall endpoint rates for adverse events. In the FOCUS trial, AEs occurred in roughly half of the enrolled patients.

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), results of the FOCUS trial at week 12 are available for fremanezumab.

In summary, in the morbidity endpoint category, the endpoints “decrease in migraine days per month by ≥ 50% and by ≥ 75 %” show statistically significant and, to a large extent, considerable advantages in favour of therapy with fremanezumab + BSC compared with placebo + BSC. This advantage is also reflected in the supplementary endpoint "mean change in headache days per month".

Health-related quality of life at week 12 for two of the three MSQoL domains showed statistically significant, clinically relevant advantages for fremanezumab + BSC over placebo

+ BSC. In addition, the endpoint "general impairment due to headache" at week 12 can be used to derive a statistically significant, clinically relevant benefit for fremanezumab + BSC versus placebo + BSC.

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

In consideration of the combined evidence presented, in the endpoint categories of morbidity and health-related quality of life, the effects of fremanezumab 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 fremanezumab 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 FOCUS trial. 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 FOCUS trial 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 due to AEs is considered low, this is considered high for the endpoints symptomatology (migraine days per month and, as a supplement, headache days/month). The symptomatology endpoint was derived from the daily entries in the electronic diary. Due to missing information, it remains unclear how complete these entries in the electronic diary were. The number of migraine days per month was calculated by extrapolating the proportion of migraine days in the days documented to all the days of the month. Many days were not documented, which may have led to significant errors in the calculation of monthly migraine days. The pharmaceutical company subsequently submitted additional information during the course of the written statements procedure on the missing entries in the electronic diary, but this was insufficient to assess their extent.

There are also still some uncertainties regarding the transferability of the study results to the context of the German health care system. 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 consideration of the combined evidence presented, the reliability of the data is sufficient to provide a hint for an additional benefit.

2.1.2 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Ajovy® with the active ingredient fremanezumab.

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, 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 suitable data for this patient group. The two pivotal studies HALO CM and HALO EM submitted by the pharmaceutical company are not suitable for assessing the additional benefit of fremanezumab compared with the appropriate comparator therapy. Both the continuation of an existing inadequate therapy, as performed in the comparator arm of both studies, and the administration of a placebo alone cannot be considered to be equivalent to implementing an appropriate comparator therapy. In consideration of the combined evidence presented, for untreated adult patients who have responded inadequately, are unable to tolerate or are unsuitable for at least one prophylactic medication, the additional benefit for fremanezumab 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 consideration of the combined evidence presented, 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 fremanezumab 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 has presented the results from a sub-population of the direct comparative RCT FOCUS (episodic and chronic migraines), performed over a double-blind period of 12 weeks.

At week 12, in the morbidity category for the endpoints “decrease in migraine days per month by ≥ 50 % and ≥ 75 %”, a statistically significant, considerable advantage can be derived for each for fremanezumab + BSC compared with placebo + BSC. This advantage is also reflected in the supplementary endpoint "mean change in headache days per month". In the health-related quality of life category, there is a statistically significant, clinically relevant benefit at week 12 for two of the three MSQoL domains and for general impairment due to headache for fremanezumab + BSC over placebo + BSC, while in the adverse events category and in overall mortality at week 12, there is no difference between fremanezumab + BSC and placebo + BSC.

In consideration of the combined evidence presented, 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 fremanezumab 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). Based on the estimations of the IQWiG addendum of 3 September 2019[5], the number of patients in all patient groups were determined on the basis of patient figures from previous resolutions in the indication[6]. 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, due to 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.

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

[5] 2nd Addendum of the IQWIG (G19-14) on the resolution on galcanezumab of 19 September 2019
[6] Resolution on erenumab of 2 May 2019, modified on 19 September 2019; resolution on galcanezumab of 19 September 2019

product characteristics, SmPC) for Ajovy® (active ingredient: fremanezumab) at the following publicly accessible link (last access: 11 September 2019):

https://www.ema.europa.eu/documents/product-information/ajovy-epar-product-information_en.pdf

Treatment with fremanezumab 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 October 2019).

It is assumed that one year will be required 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				
Fremanezumab	continuous, 1 × monthly or 1 x every 3 months	4–12	1	4–12
Best supportive care (patient population c)	no data available			

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Appropriate comparator therapy				
Patient population a)				
Amitriptyline	continuous, 1 × daily	365	1	365
Flunarizine	up to 6 months	121–146	1	121–146
Metoprolol	continuous, 1 × daily	365	1	365
Propranolol	continuous, 2–3 × daily	365	1	365
Topiramate	continuous, 2 × daily	365	1	365
Patient population b)				
Clostridium botulinum toxin type A[3]	continuously, every 12 weeks	4.3	1	4.3[7]
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 day	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Fremanezumab	225 mg	225 mg	1 × 225 mg	12	12 × 225 mg
	or				
	675 mg	675 mg	3 × 225 mg	4	12 × 225 mg
Best supportive	no data available				

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

Designation of the therapy	Dosage	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
care (patient population c)					
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
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[8] - 1,500 mg	500 mg - 1,500 mg	1 × 500 mg - 3 × 500 mg	365	365 × 500 mg - 1,095 × 500 mg
Patient population c)					
Best supportive care	no data available				

Costs:

Costs of the medicinal products:

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 costs of the medicinal products were then calculated on the basis of the costs per pack after

[8] 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

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					
Fremanezumab	3 SFI	€ 2,027.36	€ 1.77	€ 112.51	€ 1,913.08
Appropriate comparator therapy					
Patient population a)					
Amitriptyline 25 mg[9]	100 FCT	€ 18.27	€ 1.77	€ 0.58	€ 15.92
Amitriptyline 75 mg	100 TAB	€ 31.62	€ 1.77	€ 1.63	€ 28.22
Flunarizine 5 mg[9]	100 HC	€ 32.49	€ 1.77	€ 1.70	€ 29.02
Flunarizine 5 mg[9]	50 HC	€ 22.36	€ 1.77	€ 0.90	€ 19.69
Flunarizine 10 mg[9]	100 HC	€ 52.32	€ 1.77	€ 3.27	€ 47.28
Flunarizine 10 mg[9]	50 HC	€ 33.07	€ 1.77	€ 1.75	€ 29.55
Metoprolol 100 mg[9]	100 TAB	€ 13.77	€ 1.77	€ 0.22	€ 11.78
Metoprolol 200 mg[9]	100 TAB	€ 19.17	€ 1.77	€ 0.65	€ 16.75
Propranolol[9]	100 TAB	€ 19.16	€ 1.77	€ 0.65	€ 16.74
Topiramate[9]	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[8]	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: 15 October 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.

As 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

[9] Fixed amount

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 9 May 2017.

The appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 20 June 2017.

On 14 May 2019, the pharmaceutical company submitted a dossier for the benefit assessment of fremanezumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 May 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 fremanezumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 August 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 August 2019. The deadline for submitting written statements was 5 September 2019.

The oral hearing was held on 24 September 2019.

By letter dated 24 September 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 18 October 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 29 October 2019, and the proposed resolution was approved.

At its session on 7 November 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 May 2017	Determination of the appropriate comparator therapy

Subcommittee Medicinal products	20 June 2017	Redefinition of the appropriate comparator therapy
Working group Section 35a	17 September 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	24 September 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 October 2019 15 October 2019 22 October 2019	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	29 October 2019	Concluding discussion of the proposed resolution
Plenum	7 November 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 7 November 2019

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

Prof Hecken