Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Eptinezumab (prophylaxis of migraine)

of 16 February 2023

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 the 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 decides on the benefit assessment within three months of its publication. The resolution is to be published online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was 1 September 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA for the first placing on the (German) market of the active ingredient eptinezumab. 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 26 August 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 December 2022 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of eptinezumab 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 eptinezumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to 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 Eptinezumab (Vyepti) in accordance with the product information

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

Therapeutic indication of the resolution (resolution of 16.02.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine

Appropriate comparator therapy for eptinezumab for prophylaxis of migraine:

- Metoprolol or propranolol or flunarizine or topiramate or amitriptyline or clostridium botulinum toxin type A or erenumab

b) Adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A)

Appropriate comparator therapy for eptinezumab for prophylaxis of migraine:

- Erenumab or fremanezumab or galcanezumab

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 in accordance with 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 G-BA 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 the present therapeutic indication, besides eptinezumab, the active ingredients amitriptyline, flunarizine, metoprolol, propranolol and topiramate, the antibodies erenumab, galcanezumab and fremanezumab as well as clostridium botulinum toxin type A are approved for the prophylaxis of chronic migraine.

on 2. In the context of statutory health insurance, a non-medicinal treatment within the patient group defined by the therapeutic indication is not considered as an appropriate comparator therapy.

on 3. For the prophylaxis of migraine, three resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available for erenumab (resolution of 2 May 2019), galcanezumab (resolution of 19 September 2019) and fremanezumab (resolution of 7 November 2019). In addition, there is a resolution on the reassessment of erenumab due to new scientific knowledge (resolution of 21 October 2021).

For valproic acid, there are resolutions from 20 March 2020 and 18 August 2022 regarding prophylaxis of migraine in adulthood (see Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications).

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication. In this regard, it is to be noted that the robust evidence on therapeutic options in the present therapeutic indication is limited overall and no superiority of one of the active ingredients mentioned can be deduced. Therefore, of the medicinal therapy options approved in Germany, no active ingredient can be explicitly emphasised as a therapy standard in prophylaxis of migraine. On the basis of the aggregated evidence, different treatment settings are to be distinguished in prophylaxis of migraine, so that different patient populations are to be considered on the basis of the present therapy recommendations.

Patient population a) includes untreated and pre-treated patients who are eligible for conventional prophylaxis of migraine. In these patients, considering the aggregate evidence, the use of or switch to one of these options is appropriate: Metoprolol or propranolol or flunarizine or topiramate or amitriptyline or clostridium botulinum toxin type A. According to the marketing authorisation, flunarizine is only to be used if treatment with beta-receptor blockers is contraindicated or has not shown sufficient effect. Clostridium botulinum toxin type A is only approved for use in patients with chronic migraine and, moreover, even in patients with chronic migraine, it is not always appropriate for all patients.
Against the background of the revision of Annex VI to Section K of the Pharmaceuticals Directive (Prescribability of approved medicinal products in non-approved therapeutic indications) for valproic acid by resolutions of 20 March 2020 and 18 August 2022, valproic acid cannot currently be named as an appropriate comparator therapy in the therapeutic indication to be assessed here.
Fremanezumab and galcanezumab have not shown any additional benefit in patient group a).
By resolution of 20 May 2021, the G-BA carried out a new benefit assessment for the active ingredient erenumab, based on an application due to new scientific knowledge in accordance with Section 14 VerfO. For patient group a), erenumab was able to give a hint for a considerable additional benefit compared to topiramate. Therefore, erenumab is also considered an equally appropriate therapeutic alternative for patient population a). The adjustment of the appropriate comparator therapy that has now been made has no influence on the outcome of the current procedure.

In the overall assessment, for patients eligible for conventional prophylaxis of migraine, metoprolol or propranolol or flunarizine or topiramate or amitriptyline or Clostridium botulinum toxin type A or erenumab are each considered to be appropriate comparator therapy.

The appropriate comparator therapy determined here includes several therapeutic alternatives. In this context, individual therapeutic alternatives only represent a comparator therapy for the part of the patient population that has the specified patient and disease characteristics. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

In patient population b), if adult patients do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, Clostridium botulinum toxin type A), therapy with the approved antibodies erenumab or fremanezumab or galcanezumab is the indicated appropriate comparator therapy.
With erenumab, galcanezumab and fremanezumab, further medicinal products have been approved in the present therapeutic indication in recent years. Within the scope of the benefit assessment according to Section 35a SGB V, hint for a considerable additional benefit was derived for erenumab, galcanezumab and fremanezumab compared to BSC. In addition, the antibodies are considered to be established in care in the present treatment setting. Even taking into account the aggregated evidence, for adult patients who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A), it no longer seems appropriate overall to determine treatment with BSC alone as an appropriate comparator therapy. Instead, the therapeutic indication has evolved to the extent that treatment with

erenumab or fremanezumab or galcanezumab is currently considered to be an appropriate comparator therapy.
The appropriate comparator therapy determined here includes several therapeutic alternatives. These therapeutic alternatives are equally appropriate for the comparator therapy.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

a) Adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine

The additional benefit is not proven for adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine.

Justification:

The pharmaceutical company does not present data for the assessment of the additional benefit of eptinezumab compared to the appropriate comparator therapy for adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine.

b) Adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A)

The additional benefit is not proven for adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A).

Justification:

The pharmaceutical company shall submit an adjusted indirect comparison for the assessment of eptinezumab versus fremanezumab via the bridge comparator placebo for the patient population to be assessed. For the adjusted indirect comparison, the pharmaceutical company identifies the DELIVER study on the intervention side and the FOCUS study on the fremanezumab side.

The DELIVER study is a double-blind, randomised controlled trial comparing eptinezumab with placebo. It includes a 4-week screening phase, a 24-week double-blind, placebo-controlled treatment phase and a subsequent 48-week phase in which all patients received either 100 mg or 300 mg of eptinezumab. Adults with chronic or episodic migraine documented for at least 12 months and treatment failure on 2 to 4 of the following prophylactic medications in the last 10 years were enrolled: Propranolol/ metoprolol, flunarizine, amitriptyline, topiramate, candesartan, valproate/ divalproex, botulinum toxin A/B. Patients with episodic migraine had to have had an average of ≤ 14 headache days within the screening phase, of

which ≥ 4 were migraine days. Patients with chronic migraine had to have had an average of > 14 headache days within the screening phase, of which ≥ 8 were migraine days. Patients with a history of cardiovascular and neurological disease, as well as uncontrolled and/or untreated psychiatric disorders were not examined in the clinical studies of eptinezumab. A total of 892 patients were randomly assigned in the DELIVER study in a 1:1:1 ratio to treatment with 100 mg eptinezumab (N = 299), 300 mg eptinezumab (N = 294) or placebo (N = 299). According to the product information, the recommended dosage of eptinezumab is 100 mg every 12 weeks, although the need for dose escalation to 300 mg within 12 weeks of starting treatment should be assessed. As patients in the DELIVER study were randomised directly to 300 mg eptinezumab without prior dose escalation, this treatment arm is not relevant for the benefit assessment and is not considered further in the following. The pharmaceutical company shall submit the results of a sub-population of those patients who previously did not respond to or did not tolerate ≥ 2 active ingredients (metoprolol/ propranolol, flunarizine, amitriptyline, topiramate). This sub-population comprises 284 patients in the intervention arm and 287 in the comparator arm. This sub-population submitted by the pharmaceutical company is relevant for the present research question and is used for the benefit assessment.

The FOCUS study is a double-blind, randomised controlled trial comparing fremanezumab versus placebo and was already the subject of the benefit assessment of fremanezumab. The study includes a 4-week screening phase, a 12-week double-blind, placebo-controlled treatment phase and a subsequent 12-week open-label phase in which all patients received fremanezumab. Adults with chronic or episodic migraine documented for at least 12 months and treatment failure on 2 to 4 of the following product classes in the last 10 years were enrolled: Beta-blockers (metoprolol, propranolol, atenolol, bisoprolol), anticonvulsants (topiramate), tricyclic antidepressants (amitriptyline), calcium channel blockers (flunarizine), angiotensin II antagonists (candesartan), Clostridium botulinum toxin type A, valproic acid. Patients with episodic migraine had to have had an average of ≥ 6 and ≤ 14 headache days within the screening period, of which ≥ 4 were migraine days. Patients with chronic migraine had to have had an average of > 14 headache days within the screening phase, of which ≥ 8 were migraine days. In the 12-week double-blind treatment phase, patients with episodic and chronic migraine were randomly assigned in a 1:1:1 ratio to either monthly fremanezumab administration (N = 283), quarterly fremanezumab administration (N = 276) or placebo administration (N = 279). The quarterly fremanezumab administration consisted of a dose of 675 mg fremanezumab for all patients in the study. For monthly administration, the dosing scheme differed according to the presence of episodic or chronic migraine. The product information provides for either a monthly dosage of 225 mg or a quarterly dosage of 675 mg fremanezumab for all patients. Fremanezumab administration in patients with episodic migraine (total of 3 doses of 225 mg) is in accordance with the marketing authorisation. The dosing scheme of fremanezumab used in patients with chronic migraine (initial administration of 675 mg followed by 2 further 225 mg doses) differs from that described in the product information. These two dosing schemes were considered appropriate (following the EMA's assessment) in the previous benefit assessment of fremanezumab. Monthly and quarterly fremanezumab administration were considered equivalent and considered together. The pharmaceutical company uses the results of a sub-population of those patients who have previously not responded to ≥ 2 therapies (product classes) or have not tolerated them: Beta-blockers (propranolol or metoprolol), flunarizine, topiramate or amitriptyline. The sub-population includes 388 patients in the intervention arm and 195 in the comparator arm. This sub-population submitted by the pharmaceutical company is relevant for the present research question and is used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall mortality

In the DELIVER and FOCUS studies, no deaths occurred in either arm.

Morbidity

Symptomatology (migraine days per month)

In both the DELIVER study and the FOCUS study, a migraine day was defined according to the ICHD-3 criteria, which is why sufficient similarity of the operationalisations in both studies is assumed. Responder analyses were submitted for a reduction in migraine days of ≥ 50%, and ≥ 75% compared to the baseline phase, averaged over the treatment period, for both eptinezumab and fremanezumab versus placebo, respectively. Both a reduction by ≥ 50% and by ≥ 75% of the monthly migraine days are considered patient-relevant in the present therapeutic indication.

The information was recorded daily by the patients in both studies in their electronic patient diary. Since no data on the frequency or distribution of missing values in the electronic diary are available for the FOCUS study, a high risk of bias must be assumed for the endpoint "migraine days per month" in this study. Against this background, an adjusted indirect comparison for the present endpoint is inappropriate as the requirements for certainty of results for conducting an adjusted indirect comparison are not met. For this reason, the endpoint "migraine days per month" is not used for the present benefit assessment.

Symptomatology (headache days per month)

Furthermore, analyses from the DELIVER and FOCUS studies are available for headache days overall, but not differentiated by severity or type of headache. The operationalisation "change in headache days per month" compared to the baseline phase, averaged over the treatment period, is presented additionally. Evaluations on the reduction of headache days per month by ≥ 50% or ≥ 75% compared to the baseline phase are not available.

For this endpoint, too, the risk of bias in the FOCUS study is classified as high, analogous to the endpoint "migraine days per month", which is why the adjusted indirect comparison between eptinezumab and fremanezumab is not used here either.

Health status (EQ-5D VAS)

In the DELIVER and FOCUS studies, health status was assessed in a patient-reported manner using the EQ-5D visual analogue scale, on which patients answer the question about their own health status at the time of measurement. 0 stands for the worst imaginable health status and 100 for the best imaginable health status. The VAS of the EQ-5D is considered in the morbidity category for the benefit assessment.

For the endpoint of health status (EQ-5D VAS), the adjusted indirect comparison does not show any statistically significant difference between eptinezumab and fremanezumab.

Health-related quality of life

General impairment due to headache (HIT-6)

Health-related quality of life was assessed in the DELIVER and FOCUS studies using the Headache Impact Test-6 (HIT-6) instrument. This is a validated instrument to assess a patient's headache-related impairment over the past month. The severity of the impairment due to headache is assessed on a Likert scale; depending on the answer, the questions are weighted (with 6, 8, 10, 11 or 13 points) and a total score is calculated, which can range from 36 to 78. Higher values correspond to more severe impairment due to headache.

The mean differences are used for the endpoint of general impairment due to headache (HIT-6). The adjusted indirect comparison does not show any statistically significant difference between eptinezumab and fremanezumab.

Migraine-Specific Quality of Life Questionnaire (MSQoL)

Health-related quality of life was assessed in the DELIVER and FOCUS studies using the Migraine-Specific Quality of Life Questionnaire (MSQoL), which measures the impact of migraine on health-related quality of life within the past 4 weeks and is composed of three domains: role function-restrictive (RFR; 7 items), role function-preventive (RFP; 4 items) and emotional function (EF; 3 items). The RFR domain asks about the extent of migraine-related limitation of everyday activities, work, interaction with family and friends, as well as with regard to the ability to concentrate and energy. The RFP domain provides information about the extent of the migraine-related limitation with regard to participation in social activities, everyday activities and work. In the EF domain, the influence of migraine on the psychological well-being of the patients is recorded. The severities are surveyed using a Likert scale. A higher value corresponds to a better health-related quality of life.

There was no statistically significant difference between eptinezumab and fremanezumab in the adjusted indirect comparison for the domains role function-restrictive and emotional function. For the domain role function-preventive, the adjusted indirect comparison shows a statistically significant difference to the advantage of eptinezumab. However, the 95% confidence interval of the standardised mean difference (SMD) is not completely outside the irrelevance range between –0.2 and 0.2. Thus, it cannot be inferred with sufficient certainty that the effect is clinically relevant.

Side effects

SAEs and discontinuation due to AEs

For the endpoints of SAEs and discontinuation due to AEs, the adjusted indirect comparison does not show any statistically significant difference between eptinezumab and fremanezumab.

Overall assessment/ conclusion

For prophylaxis of migraine in adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A), the results of the DELIVER (eptinezumab vs placebo) and FOCUS (fremanezumab vs placebo) as well as the adjusted indirect comparison of eptinezumab vs fremanezumab via the bridge comparator placebo are available for the benefit assessment of eptinezumab. This adjusted indirect comparison allows comparative statements for eptinezumab versus fremanezumab over a period of 12 weeks.

No events occurred in the mortality category during both studies.

In the endpoint category of morbidity, the results of the adjusted indirect comparison for the endpoint "migraine days per month" cannot be used as the methodological requirements for this are not met due to the high risk of bias of this endpoint in the FOCUS study. For the endpoint "health status (EQ-5D VAS)", the adjusted indirect comparison does not show any statistically significant differences between eptinezumab and fremanezumab. In the endpoint category of health-related quality of life, there was also no statistically significant difference between eptinezumab and fremanezumab in the HIT-6 as well as in the domains "Role Function-Restrictive" and "Emotional Function" of the MSQoL. For the domain "Role Function-

Preventive" of the MSQoL, there is a statistically significant but not clinically relevant difference in favour of eptinezumab.

In the category of side effects, no advantages or disadvantages can be derived for eptinezumab compared to fremanezumab on the basis of the adjusted comparison.

Overall, in the endpoint categories of morbidity, health-related quality of life and side effects, there were neither relevant positive nor negative effects for eptinezumab versus fremanezumab in the adjusted indirect comparison at week 12. An additional benefit of eptinezumab for adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A) is thus not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Vyepti with the active ingredient eptinezumab.

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

The following patient populations were distinguished for the benefit assessment:

a) Adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine

b) Adults who have at least 4 migraine days per month and who do not respond to, are ineligible for, or are intolerant to any of the medicinal therapies/ product classes (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A)

Patient population a)

The G-BA determined therapy with metoprolol or propranolol or flunarizine or topiramate or amitriptyline or Clostridium botulinum toxin type A or erenumab as an appropriate comparator therapy.

The pharmaceutical company does not present any data for the assessment of the additional benefit in this patient population. Thus, an additional benefit of eptinezumab compared with the appropriate comparator therapy for adults who have at least 4 migraine days per month and are eligible for conventional prophylaxis of migraine is not proven.

Patient population b)

The G-BA determined therapy with erenumab or fremanezumab or galcanezumab as the appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company presents an adjusted indirect comparison of eptinezumab (DELIVER study) vs fremanezumab (FOCUS study) via the bridge comparator placebo at week 12.

In summary, there is no statistically significant difference in mortality at week 12. Also in the morbidity category, the indirect comparison does not show any statistically significant difference between eptinezumab and fremanezumab. The results of the indirect comparison for the endpoint "migraine days per month" cannot be used here as the methodological requirements for this are not met due to the high risk of bias of this endpoint in the FOCUS

study. In the quality of life category, there is a statistically significant difference in favour of eptinezumab in the domain "Role Function-Preventive" of the MSQoL, which, however, has no clinical relevance. In the category of side effects, no advantages or disadvantages relevant for the benefit assessment can be derived.

In the overall assessment, there are no advantages or disadvantages of eptinezumab compared with the appropriate comparator therapy fremanezumab. An additional benefit is not proven.

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

The number of patients is based on the target population in statutory health insurance (SHI).

The data are based on patient numbers, which are supported by the information provided by the pharmaceutical company from the written statement, taking into account the patient numbers derived in the previous resolutions regarding the therapeutic indication[2] as well as on current sources on prevalence. The number of patients in the SHI target population is in a plausible order of magnitude, even if these figures are subject to uncertainties.

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 Vyepti (active ingredient: eptinezumab) at the following publicly accessible link (last access: 11 January 2023):

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

Treatment with eptinezumab should only be initiated and monitored by doctors experienced in migraine therapy.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2023).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

For flunarizine, costs are shown for 6 months, as the product information limits the use 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 starting 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 starting dose should not be given for longer than is necessary for symptom relief (usually no longer than two months). For the maintenance

2 Resolutions on erenumab dated 2 May 2019, as amended 19 September 2019 and 21 October 2021; resolution on galcanezumab dated 19 September 2019. resolution on fremanezumab dated 7 November 2019.

dose, the daily dose should be reduced by taking flunarizine either only every other day or for 5 consecutive days followed by two treatment-free days. A range is shown for the treatment costs of flunarizine taking into account the data; the lower limit of the range is calculated from the initial dose 5 mg once daily followed by a maintenance dose every other day, while the upper limit of the range is calculated from 10 mg daily taking into account a maintenance dose 5 days of flunarizine followed by two treatment-free days. Treatment with flunarizine should be stopped after 6 months at the latest and should only be resumed if the treated symptoms return. Only 6 months of treatment duration are used for the calculation. Notwithstanding this, the costs may be higher if treatment with flunarizine is started again 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				
Eptinezumab	Continuously, every 84 days	4.3	1	4.3
Appropriate comparator therapy				
Patient population a)				
Amitriptyline	Continuously, 1 x daily	365	1	365
Flunarizine	Up to 6 months	121-146	1	121-146
Metoprolol	Continuously, 1 x daily	365	1	365
Propranolol	Continuously, 2-3 x daily	365	1	365
Topiramate	Continuously, 2 x daily	365	1	365
Erenumab	Continuously, 1 x every 28 days	13	1	13
Clostridium botulinum toxin type A[3]	Continuously, every 84 days	4.3	1	4.3
Patient population b)				
Erenumab	Continuously, 1 x every 28 days	13	1	13
Fremanezumab	Continuously, 1 x monthly or every 3 months	4-12	1	4-12
Galcanezumab	Continuously, 1 x monthly	12	1	12

3 According to the marketing authorisation only for chronic migraine.

Consumption:

In general, initial induction regimens are not taken into account for the cost representation, since 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/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Eptinezumab	100 mg - 300 mg	100mg - 300mg	1 x 100 mg - 3 x 100 mg	4.3	4.3 x 100 mg - 12.9 x 100 mg
Appropriate comparator therapy					
Patient population a)					
Amitriptyline	25 mg - 75 mg	25mg - 75mg	1 x 25 mg - 1 x 75 mg	365	365 x 25 mg - 365 x 75 mg
Flunarizine	5 mg - 10 mg	5mg - 10mg	1 x 5 mg - 1 x 10 mg	121-146	121 x 5 mg - 146 x 10 mg
Metoprolol	100 mg - 200 mg	100mg - 200mg	100 mg - 200 mg	365	365 x 100 mg - 365 x 200 mg
Propranolol	40 mg	80 mg - 120 mg	2 x 40 mg - 3 x 40 mg	365	730 x 40 mg - 1095 x 40 mg
Topiramate	50 mg	100 mg	2 x 50 mg	365	730 x 50 mg
Clostridium botulinum toxin type A[2]	155 - 195 units	155 - 195 units	2 x 100 units	4.3	8.6 x 100 units
Erenumab	70 mg - 140 mg	70 mg - 140 mg	1 x 70 mg - 1 x 140 mg	13	13 x 70 mg - 13 x 140 mg
Patient population b)					
Erenumab	70 mg - 140 mg	70 mg - 140 mg	1 x 70 mg - 1 x 140 mg	13	13 x 70 mg - 13 x 140 mg
Fremanezumab	225 mg	225 mg	1 x 225 mg	12	12 x 225 mg
	or				
	675 mg	675 mg	3 x 225 mg	4	12 x 225 mg
Galcanezumab	120 mg	120 mg	1 x 120 mg	12	12 x 120 mg

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 sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 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 deduction of the statutory rebates. If a fixed reimbursement rate is available, this will be used as the basis for calculating the costs.

Designation of the therapy	Packaging 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					
Eptinezumab	1 CIS	€ 1,392.65	€ 2.00	€ 131.11	€ 1,259.54
Appropriate comparator therapy					
Patient population a)					
Amitriptyline 25 mg[4]	100 FCT	€ 18.56	€ 2.00	€ 0.58	€ 15.98
Amitriptyline 75 mg[4]	100 FCT	€ 29.70	€ 2.00	€ 1.46	€ 26.24
Flunarizine 5 mg[4]	100 HC	€ 32.78	€ 2.00	€ 1.70	€ 29.08
Flunarizine 5 mg[4]	50 HC	€ 22.66	€ 2.00	€ 0.90	€ 19.76
Flunarizine 10 mg[4]	100 HC	€ 52.62	€ 2.00	€ 3.27	€ 47.35
Flunarizine 10 mg[4]	50 HC	€ 33.37	€ 2.00	€ 1.75	€ 29.62
Metoprolol 100 mg[4]	100 TAB	€ 14.07	€ 2.00	€ 0.22	€ 11.85
Metoprolol 200 mg[4]	100 RET	€ 19.47	€ 2.00	€ 0.65	€ 16.82
Propranolol[4]	100 TAB	€ 19.46	€ 2.00	€ 0.65	€ 16.81
Topiramate[4]	200 FCT	€ 83.63	€ 2.00	€ 5.72	€ 75.91
Clostridium botulinum toxin type A	3 x 100 units PSI	€ 1,300.67	€ 2.00	€ 122.38	€ 1,176.29
Erenumab 70 mg	3 SFI	€ 913.28	€ 2.00	€ 35.67	€ 875.61
Erenumab 140 mg	3 SFI	€ 913.28	€ 2.00	€ 35.67	€ 875.61
Patient population b)					
Erenumab 70 mg	3 SFI	€ 913.28	€ 2.00	€ 35.67	€ 875.61
Erenumab 140 mg	3 SFI	€ 913.28	€ 2.00	€ 35.67	€ 875.61
Fremanezumab	3 SFI	€ 1,312.25	€ 2.00	€ 51.45	€ 1,258.80
Galcanezumab	3 SFI	€ 1,465.34	€ 2.00	€ 138.01	€ 1,325.33
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder for solution for injection; RET = retard tablets; TAB = tablets					

4 Fixed reimbursement rate

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 the standard expenditure in the course of the treatment are not shown.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Eptinezumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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

At its session on 6 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 26 August 2022, the pharmaceutical company submitted a dossier for the benefit assessment of eptinezumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 August 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 eptinezumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 23 November 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 December 2022. The deadline for submitting written statements was 22 December 2022.

The oral hearing was held on 9 January 2023.

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 was discussed at the session of the subcommittee on 7 February 2023, and the proposed resolution was approved.

At its session on 16 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 October 2020	Determination of the appropriate comparator therapy
Working group Section 35a	4 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 January 2023	Conduct of the oral hearing
Working group Section 35a	18 January 2023 1 February 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	7 February 2023	Concluding discussion of the draft resolution
Plenum	16 February 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 February 2023

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

Prof. Hecken