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
Erenumab (Reassessment due to New Scientific Knowledge)

of 21 October 2021

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 studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

After the active ingredient erenumab (Aimovig) was first placed on the market on 1 November 2018, the G-BA conducted a benefit assessment of this active ingredient in accordance with Section 35a SGB V and passed a resolution on erenumab on 2 May 2019.

In its session on 4 March 2021, the G-BA decided to grant the pharmaceutical company a new benefit assessment based on their request, according to Section 35a paragraph 5 SGB V.

The approval of the request was linked to the condition that the new benefit assessment is carried out on the basis of a data basis corresponding to the currently generally accepted state of medical-scientific knowledge, including the HER-MES study for patient population a (patients eligible for conventional prophylaxis of migraine).

By decision of 4 March 2021, the pharmaceutical company was requested to submit the evidence required for the benefit assessment pursuant to Section 35a, paragraph 1, sentence 3 SGB V within three months of the notification of the decision under point I.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on the date. 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 2 August 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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 erenumab (Aimovig) in accordance with the product information

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

Therapeutic indication of the resolution (resolution from 21.10.2021):

Prophylaxis of migraine in adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine.

Appropriate comparator therapy for erenumab for prophylaxis of migraine:

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

1 General Methods, version 6.0 from 05.11.2020. 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 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 Federal Joint Committee has already determined the patient-relevant benefit 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, 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).
For valproic acid, there is a resolution of 20 March 2020 regarding prophylaxis of migraine in adults (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 therapeutic standard in the prophylaxis of migraine. On the basis of

the aggregated evidence, different treatment situations are to be distinguished in the 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 in the group a.
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 are each considered equally appropriate therapeutic alternatives, taking into account the marketing authorisation and previous therapy.
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 resolution of 20 March 2020, valproic acid cannot currently be named as an appropriate comparator therapy in the therapeutic indication to be assessed here.

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

2.1.3 Extent and probability of the additional benefit

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

For prophylaxis of migraine in adults with at least 4 migraine days per month eligible for conventional migraine prophylaxis, there is a hint for a considerable additional benefit of erenumab compared with the appropriate comparator therapy topiramate.

Justification:

The HER-MES study was submitted to evaluate the additional benefit of erenumab for prophylaxis of migraine in adults with at least 4 migraine days per month who are eligible for conventional prophylaxis of migraine.
The HER-MES study is a randomised, double-blind, parallel-group RCT comparing erenumab with topiramate over a 24-week period in adult patients with at least 4 migraine days per month in at least two different migraine attacks. Included adults had an average of 10 migraine days per month and were either therapy naïve for migraine (approximately 60% of study participants) or had not responded to or were ineligible for up to three of the following active ingredients for prophylaxis of migraine: Metoprolol/propranolol, amitriptyline, or

flunarizine. Baseline characteristics of the study population indicate that the non-therapy-naïve patients in the study had previously failed at least one prophylaxis of migraine.

Patients were treated in the erenumab arm for an average of 21.8 weeks and in the topiramate arm for an average of 16.5 weeks and were followed until the end of the study. The primary endpoint of the study was treatment discontinuations due to adverse events (AEs). Additional endpoints included overall mortality and endpoints in the categories of morbidity, health-related quality of life, and side effects. The present benefit assessment is based on the evaluations of the total population of the HER-MES study at week 24.

A total of 777 patients were randomised in the study at a 1:1 ratio to either treatment with erenumab (N = 389) or treatment with topiramate (N = 388). Patients in the HER-MES study received the highest individually tolerated dose of erenumab or topiramate. In the erenumab arm, patients received 70 mg or 140 mg of erenumab every 4 weeks for 24 weeks. In the topiramate arm, patients received 50 mg to 100 mg topiramate for 18 weeks after a 6-week titration phase. In addition, the patients in both study arms received corresponding placebo preparations for the purpose of blinding. While topiramate therapy provided the option to extend dose titration if adverse events occurred or to reduce the target dose, once reached, the dose of topiramate (and erenumab) could not be reduced again during the study.

After premature discontinuation of treatment, patients should remain in the study and complete their migraine diary. Although the use of other migraine prophylaxis as a subsequent therapy was not planned, those who discontinued therapy were allowed to take migraine acute medication.

Patients enrolled in the HER-MES study had an average of 11 headache days and 10 migraine days per month at the start of the study. Based on the study characteristics presented at baseline, it is not possible to determine the percentage of patients with chronic or episodic migraine. Chronic migraine is defined by ICHD-3 as a headache on more than 15 days per month for a period of more than 3 months, with a headache on at least 8 days fulfilling the criteria for migraine. Episodic migraine, on the other hand, is defined as up to 14 migraine days per month.

Extent and probability of the additional benefit

Mortality

Overall mortality

In the HER-MES study, no deaths occurred in either study arm.

Morbidity

Symptomatology (migraine days per month)

In the HER-MES study, a migraine day was defined as a calendar day on which a patient documented a migraine headache. Migraine headache, in turn, was defined as migraine with or without aura for a period of at least 30 minutes that also met ICHD-3 classification criteria for pain intensity and/or use of acute medication. Pain is considered relevant to the patient.

For the endpoint "migraine days per month", responder analyses for reduction of ≥ 50% over the last three months and over the first month were considered relevant and used.

There was a statistically significant difference in the benefit of erenumab over topiramate for both the last three months and the first month.

Health-related quality of life

General impairment due to headache (HIT-6) - improvement of ≥ 5 or ≥ 6.3 points

Health-related quality of life was assessed in the HER-MES study 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 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 headaches.

In the dossier, the pharmaceutical company presented analyses of the percentage of patients with an improvement in the HIT-6 total score by ≥ 5 points each and by ≥ 6.3 points each.
According to IQWiG's current methodological approach (Methods 6.0, published on 05.11.2020[2]), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of precisely 15% of the scale range) to be necessary for patient-reported endpoints to represent a noticeable change with sufficient certainty. The G-BA has already recognised a response threshold of ≥ 5 points as a clinically relevant change in HIT-6 in the present indication. Therefore, against the background of the current methodological discussion, both the responder analysis with a response threshold of 15% (here ≥ 6.3 points) and the responder analysis with a response threshold of ≥ 5 points are used to assess the additional benefit. The methodological discussion on the further procedure in the G-BA has not yet been concluded.

For the endpoint "general impairment due to headache", there is a statistically significant advantage for erenumab over topiramate for an improvement of ≥ 5 points in the HIT-6. Responder analysis on the 15% scale range (improvement by ≥ 6.3 points in the HIT-6) also showed a statistically significant advantage in favour of erenumab over topiramate.

SF-36v2 - physical and mental component scores (improvement SF-36 by ≥ 5 and 9.4 and 9.6 points, respectively)

The Health Survey Short Form 36 (SF-36) is a generic instrument for measuring health-related quality of life, consisting of 8 domains and a total of 36 questions. The physical sum scale (PCS) and the mental sum scale (MCS) of the generic quality-of-life questionnaire SF-36 were used in the assessment.

According to IQWiG's current methodological approach (Methods 6.0, published on 05.11.2021**Fehler! Textmarke nicht definiert.**[2]), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of precisely 15% of the scale range) to be necessary for patient-reported endpoints to represent a noticeable change with sufficient certainty. For the SF-36, the G-BA has recognised a response threshold of ≥ 5 points as a clinically relevant change in previous benefit assessment procedures in the present indication. Therefore, against the background of the current methodological discussion, both the responder analysis with a response threshold of 15% (here ≥ 9,4 and 9.6 points, respectively) and the responder analysis with a response threshold of ≥ 5 points are used to assess the additional benefit. The methodological discussion on the further procedure in the G-BA has not yet been concluded.

For the endpoint "health-related quality of life", a statistically significant advantage for erenumab over topiramate is shown for the improvement by ≥ 5 points in the SF-36 for both the physical and the mental sum score. For the responder analysis on the 15% scale range (improvement of ≥ 9.4 points in the SF-36 PCS and improvement by ≥ 9.4 points in the SF-36 MCS, respectively), however, there was no statistically significant difference between erenumab and topiramate.

Side effects

SAE

For the endpoint SAE, there was no statistically significant difference between the treatment groups erenumab and topiramate at week 24.

Discontinuation because of AEs

For the endpoint discontinuation due to AEs, there is a statistically significant advantage at week 24 in favour of erenumab over topiramate.

Specific AEs

For the endpoint nervous system disorders and the events paresthesia, attention deficit and dizziness included therein as well as for the endpoints nausea, fatigue and appetite decreased, a statistically significant difference to the advantage of erenumab over topiramate was shown in each case. For the endpoint constipation (PT, AE), on the other hand, there is a statistically significant difference to the disadvantage of erenumab.

Overall assessment

The results of the HER-MES study are available for the renewed benefit assessment of erenumab for prophylaxis of migraine in adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine. This study allows comparative statements for erenumab versus topiramate over a period of 24 weeks.

2 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne. https://www.iqwig.de/de/methoden/methodenpapier.3020.html

In summary, statistically significant advantages for erenumab over topiramate are shown in the endpoint categories morbidity for the endpoints on "migraine days per month" as well as in health-related quality of life at week 24 in both the generic SF-36 and the HIT-6, which are rated as considerable.

In the category of side effects, statistically significant advantages can also be derived for erenumab compared to the appropriate comparator therapy topiramate at week 24. Thus, for the endpoint discontinuation due to AEs, there is a statistically significant, considerable advantage in favour of erenumab over topiramate, while no advantages or disadvantages can be derived for the overall rate of SAEs. The overall benefit seen in the category side effects is confirmed by the results for specific AEs. No events occurred in the mortality category during the study.

In the overall assessment, the endpoint categories morbidity, health-related quality of life, and side effects for erenumab compared with the appropriate comparator therapy in the study at week 24 were exclusively positive effects, which were not offset by any relevant negative results from other categories.

Based on these considerations, the information in the dossier and the results of the benefit assessment, the G-BA considers the additional benefit of erenumab compared with the appropriate comparator therapy topiramate in adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine to be a previously unachieved significant improvement in the therapy-relevant benefit and classifies the extent of the additional benefit as considerable.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the randomised, double-blind Phase IV HER-MES study.

The risk of bias is rated as low for the HER-MES study presented at the study level. The risk of bias of the results at the endpoint level is also rated as low.

Regardless of this, uncertainties remain regarding the transferability of the study results to the German health care context.

Although it was possible during therapy with topiramate to extend the dose titration if adverse events occurred or to reduce the target dose to the target range between 50 and 100 mg, the dose of topiramate, once reached, could not be reduced again during the study. No specific guidelines or limitations on dose reduction are defined in the respective product information. The dose reduction (of both topiramate and erenumab), which was generally not permitted in the study, meant that the principal investigator's options for action were limited if adverse events occurred. The discontinuation rate was particularly high in the topiramate arm, where 39% of patients discontinued treatment prematurely (vs 11% in the erenumab arm). The main reason given for discontinuing therapy was the occurrence of adverse events. This suggests that the results - especially for the primary endpoint of the study, "discontinuation due to AEs"

- were also influenced by the lack of a dose reduction option in favour of therapy with erenumab. Overall, the disallowed dose reduction results in uncertainties regarding the reliability of the results.

In addition, the different treatment durations in the two study arms of the HER-MES study result in further limitations of the reliability of the data. In the study, no subsequent therapy in the sense of other prophylaxis of migraine was planned after premature discontinuation of treatment. Although patients were to remain in the study and complete their migraine diary in the event of premature discontinuation of treatment, the use of other prophylaxis of migraine as a subsequent therapy was not permitted. The patients were only allowed to continue their therapy for the treatment of acute migraine attacks. It should be emphasised at this point that the patients in the topiramate arm predominantly discontinued therapy during the first 6 weeks of the study. Thus, these patients did not receive prophylaxis of migraine therapy for a long period of the study. Due to the widely varying treatment durations, there are overall uncertainties with regard to the significance of the results.

In the overall assessment, relevant uncertainties remain with regard to the transferability of the study results to the German health care context, so that in the overall assessment with regard to the reliability of data, a hint for an additional benefit is derived.

2.1.4 **Summary of the assessment**

The present assessment is a new benefit assessment of the medicinal product Aimovig with the active ingredient erenumab based on an application due to new scientific knowledge according to Section 14 VerfO.

Aimovig is approved for migraine prophylaxis in adults with at least 4 migraine days per month. However, the present assessment refers only to the patient population: ""Adults with at least 4 migraine days per month eligible for conventional prophylaxis of migraine."

The G-BA determined the active ingredients metoprolol, propranolol, flunarizine, topiramate, amitriptyline or clostridium botulinum toxin type A as appropriate comparator therapies.

For the reassessment, the pharmaceutical company submitted the results of the HER-MES RCT comparing erenumab versus topiramate.

In summary, statistically significant advantages for erenumab over topiramate are shown in the endpoint categories morbidity for the endpoints on "migraine days per month" as well as in the health-related quality of life at week 24 in both the generic SF-36 and the HIT-6, which are rated as considerable. In the category of side effects, statistically significant advantages can also be derived for erenumab compared to the appropriate comparator therapy topiramate at week 24. Thus, for the endpoint discontinuation due to AEs, there is a statistically significant, considerable advantage in favour of erenumab over topiramate, while no advantages or disadvantages can be derived for the overall rate of SAEs. No events occurred in the mortality category during the study. However, uncertainties remain with regard to the transferability of the study results to the German health care context.

In the overall assessment, a hint for a considerable additional benefit of erenumab compared to the appropriate comparator therapy topiramate is derived.

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). For the group of patients that is the subject of this resolution, the numbers provided by the pharmaceutical company are used as a basis. The patient numbers in the overall assessment are subject to uncertainties.

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

The data are based on patient numbers, which are based on the information provided by the pharmaceutical company in the dossier, taking into account the patient numbers derived in the previous resolutions regarding the therapeutic indication[3] 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 Aimovig (active ingredient: erenumab) at the following publicly accessible link (last access: 9 August 2021):
https://www.ema.europa.eu/en/documents/product-information/aimovig-epar-product-information_en.pdf

Treatment with erenumab should only be initiated and monitored by doctors experienced in diagnosing and treating 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: 1st October 2021).

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 is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient or patent/year", time intervals between individual treatments and for 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

3 Resolution on erenumab dated 2 May 2019, as amended 19 September 2019; resolution on galcanezumab dated 19 September 2019. resolution on fremanezumab dated 7 November 2019.

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 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 therapy 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 or patient//year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Erenumab	continuously, every 28 days	13	1	13
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 times daily	365	1	365
Topiramate	continuously, 2 x daily	365	1	365
Clostridium botulinum toxin type A[4]	continuously, every 84 days	4.3	1	4.3

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	Dose/ patient/ or patient/ treatment day	Usage by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Erenumab	70 mg - 140 mg	70 mg - 140 mg	1x 70 mg - 1x 140 mg	13	13 x 70 mg - 13 x 140 mg
Appropriate comparator therapy					
Patient population a)					
Amitriptyline	25 mg - 75 mg	25 mg - 75 mg	1 x 25 mg - 1 x 75 mg	365	365 x 25 mg - 365 x 75 mg
Flunarizine	5 mg - 10 mg	5 mg - 10 mg	1 x 5 mg - 1 x 10 mg	121 - 146	121 x 5 mg - 146 x 10 mg
Metoprolol	100 mg - 200 mg	100 mg - 200 mg	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[4]	155 - 195 units	155 - 195 units	2 x 100 units	4.3	8.6 x 100 units

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. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on 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.

4 According to the marketing authorisation only for chronic migraine.

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					
Erenumab 70 mg	3 SFI	€ 1,465.10	€ 1.77	€ 80.51	€ 1,382.82
Erenumab 140 mg	3 SFI	€ 1,465.10	€ 1.77	€ 80.51	€ 1,382.82
Appropriate comparator therapy					
Patient population a)					
Amitriptyline 25 mg[5]	100 FCT	€ 18.33	€ 1.77	€ 0.58	€ 15.98
Amitriptyline 75 mg[5]	100 FCT	€ 29.46	€ 1.77	€ 1.46	€ 26.23
Flunarizine 5 mg[5]	100 HC	€ 32.55	€ 1.77	€ 1.70	€ 29.08
Flunarizine 5 mg[5]	50 HC	€ 22.42	€ 1.77	€ 0.90	€ 19.75
Flunarizine 10 mg[5]	100 HC	€ 52.38	€ 1.77	€ 3.27	€ 47.34
Flunarizine 10 mg[5]	50 HC	€ 33.13	€ 1.77	€ 1.75	€ 29.61
Metoprolol 100 mg[5]	100 TAB	€ 13.83	€ 1.77	€ 0.22	€ 11.84
Metoprolol 200 mg[5]	100 RET	€ 19.23	€ 1.77	€ 0.65	€ 16.81
Propranolol[5]	100 TAB	€ 19.22	€ 1.77	€ 0.65	€ 16.80
Topiramate[5]	200 FCT	€ 83.40	€ 1.77	€ 5.72	€ 75.91
Clostridium botulinum toxin type A	3 x 100 units PIE	€ 1,261.67	€ 1.77	€ 69.24	€ 1,190.66
Abbreviations: FCT = film-coated tablets, HC = hard capsules;SFI = solution for injection; PIE = powder for concentrate for solution for infusion; RET = retard tablets; TAB = tablets					

LAUER-TAXE® last revised: 1st October 2021

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

5 Fixed reimbursement rate

must be taken into account as costs for additionally required SHI services.

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

Because there are no regular differences in the necessary 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.

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 7 November 2017, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 April 2021, the pharmaceutical company submitted a dossier for the benefit assessment of erenumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 4 VerfO.

By letter dated 3 May 2021, in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient erenumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 July 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 2 August 2021. The deadline for submitting written statements was 23 August 2021.

The oral hearing was held on 6 September 2021.

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 12 October 2021, and the proposed resolution was approved.

At its session on 21 October 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	9 June 2020	Determination of the appropriate comparator therapy
Working group Section 35a	31 August 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 September 2021	Conduct of the oral hearing
Working group Section 35a	14 September 2021 21 September 2021 5 October 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	12 October 2021	Concluding discussion of the draft resolution
Plenum	21 October 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 October 2021

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

Prof. Hecken