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Erenumab (migraine) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Erenumab (Migräne) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIT	Headache Impact Test
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
PCS	Physical Component Summary
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form (36) – version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug erenumab. The company submitted a dossier for the early benefit assessment of the drug to be assessed for the first time on 29 October 2018. The company now requested a new benefit assessment for a subpopulation of the approved therapeutic indication because of new scientific findings. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 3 May 2021.

Research question

The aim of the present report was to assess the added benefit of erenumab in comparison with topiramate as appropriate comparator therapy (ACT) for the prophylaxis of migraine in patients who have at least 4 migraine days per month.

The specification of the ACT results in 2 subpopulations for the approved therapeutic indication of erenumab. Only the subpopulation of patients for whom conventional migraine prophylaxis is an option is relevant for the present assessment. The G-BA specified the ACT presented in Table 2 for this subpopulation. The subpopulation of patients who do not respond to any of the drug therapies/drug classes mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, Clostridium botulinum toxin type A), for whom these are not suitable or who cannot tolerate them, is not the subject of the present benefit assessment.

Table 2: Research question of the benefit assessment of erenumab

Therapeutic indication	**ACT**[a]
Adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis[b]	Metoprolol or propranolol or flunarizine or **topiramate** or amitriptyline or clostridium botulinum toxin type A under consideration of approval and prior therapy

a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. This population was only a subpopulation of the approved therapeutic indication and comprised pretreated and treatment-naive patients. The subpopulation of patients who do not respond to any of the drug therapies/drug classes mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, Clostridium botulinum toxin type A), for whom these are not suitable or who cannot tolerate them, is not the subject of the present benefit assessment.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the specification of the ACT and chose topiramate from the cited options. The assessment was conducted by means of patient-relevant outcomes on the basis of

the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum treatment duration of 12 weeks were used for the derivation of the added benefit.

Study pool and study design

The study pool for the present benefit assessment consists of the study HER-MES.

The HER-MES studies is a randomized, double-blind study that compares erenumab with topiramate. The study included adult patients with at least 4 migraine days per month in at least 2 different migraine attacks, who were either treatment-naive or had not responded to up to 3 of the following migraine prophylaxes, or for whom these drugs were not suitable: metoprolol/propranolol, amitriptyline or flunarizine.

A total of 777 patients were randomly allocated in a 1:1 ratio to treatment either with erenumab (N = 389) or with topiramate (N = 388). With the exception of the prohibited dose reduction (see below), the use of erenumab and topiramate in the study corresponded to the recommendations of the respective SPCs.

In the HER-MES study, patients received the highest individually tolerated dose of erenumab or topiramate. In the topiramate arm, it was possible to extend the dose titration or to reduce the target dose if adverse events (AEs) occurred. However, the dose of topiramate (and erenumab) once reached was not allowed to be reduced again during the study. If AEs occur, this represents a restriction in the investigator's options for action, which may have influenced the rate of discontinuations due to AEs.

The company stated that patients in the topiramate arm most frequently discontinued treatment during the first 6 weeks. After the patients had discontinued the treatment, they were to remain in the study and complete their migraine diary. However, intake of other migraine prophylaxes as subsequent therapy was not allowed. Consequently, patient who discontinued treatment received no migraine prophylaxis over a prolonged period in the study.

In summary, it is unclear whether and to what extent the prohibited dose reduction influenced the AEs and the discontinuation rates in the study. In addition to the outcomes mentioned, it is also unclear for the other outcomes how large the influence on the corresponding effects of erenumab would be compared to the ACT if the patients who discontinued therapy would had received a subsequent therapy. This uncertainty was taken into account in the interpretation of the study results.

In the erenumab arm, patients were treated 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.

Primary outcome of the study was “discontinuations due to AEs”. Patient-relevant secondary outcomes were all-cause mortality and outcomes of the categories of morbidity, health-related quality of life and AEs.

Risk of bias

The risk of bias across outcomes was rated as low for the results of the HER-MES study. The risk of bias for the results on all outcomes was also rated as low.

Transferability of the study results to the German health care context

The high discontinuation rate in the HER-MES study (especially in the topiramate arm) reflects the low adherence of patients in everyday practice. However, the high discontinuation rates may also be due to the study design. In everyday practice, patients who discontinue a prophylactic treatment also have the option of a subsequent therapy. However, in the HER-MES study, no prophylactic follow-up therapy was allowed after discontinuation of treatment. As described above, the comparison of erenumab with the ACT is potentially influenced by the lack of an option for dose reduction option in case of AEs and the lack of subsequent therapy after discontinuation of the study medication. Therefore, the result of the benefit assessment can only be transferred to the German health care context to a limited extent.

Results

All-cause mortality

No deaths occurred in the course of the study. There was no hint of an added benefit of erenumab in comparison with topiramate for the outcome "all-cause mortality"; an added benefit is therefore not proven.

Morbidity

Symptoms (migraine days/month; reduction by ≥ 50%)

There is a statistically significant difference in favour of erenumab versus topiramate both for the period of the last 3 months and for the period of the first month. This resulted in an indication of an added benefit of erenumab in comparison with topiramate for the outcome “symptoms (migraine days/month)”.

General impairment from headache (Headache Impact Test-6 [HIT-6]; improvement by ≥ 6.3 points)

A statistically significant difference was shown in favour of erenumab versus topiramate. This resulted in an indication of an added benefit of erenumab in comparison with topiramate for the outcome “general impairment from headache (HIT-6)”.

Health-related quality of life

Short Form (36) – version 2 Health Survey (SF-36v2) – Physical and Mental Component Summary (improvement by ≥ 9.4 points or by ≥ 9.6 points respectively)

A statistically significant difference between the treatment groups was found neither for the Physical Component Summary (PCS) nor for the Mental Component Summary (MCS). There was no hint of an added benefit of erenumab in comparison with topiramate for the outcome "health-related quality of life (SF-36v2)"; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from erenumab in comparison with topiramate; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference in favour of erenumab was shown for the outcome "discontinuation due to AEs". This resulted in an indication of lesser harm from erenumab in comparison with topiramate.

Specific AEs

Nervous system disorders (including: paraesthesia, disturbance in attention, dizziness), nausea, fatigue, decreased appetite

There was a statistically significant difference in favour of erenumab for the outcome “nervous system disorders” and the events “paraesthesia”, “disturbance in attention” and “dizziness” included therein, as well as for the outcomes “nausea”, “fatigue” and “decreased appetite”. This resulted in an indication of lesser harm from erenumab versus topiramate for the outcome “nervous system disorders” and the events “paraesthesia”, “disturbance in attention” and “dizziness” included therein, as well as for each of the outcomes “nausea”, “fatigue” and “decreased appetite”.

Constipation

A statistically significant difference to the disadvantage of erenumab was shown for the outcome "constipation". For the outcome “constipation”, this resulted in an indication of greater harm from erenumab in comparison with topiramate.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug erenumab in comparison with the ACT are assessed as follows:

Overall, there are several positive effects and one negative effect. On the side of the positive effects, there are indications of major or considerable substantial added benefit of erenumab compared to topiramate for the serious/severe symptoms/late complications. Moreover, for the

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

non-serious/not severe side effects, there are indications of lesser harm in several outcomes, the majority with the extent “considerable”. In contrast, a negative effect with the extent “considerable” was shown for the non-serious/non-severe side effects.

As described above, it is unclear whether and to what extent the prohibited dose reduction influenced the AEs and the discontinuation rates in the study. In addition to the outcomes mentioned, it is also unclear for the other outcomes how large the influence on the corresponding effects of erenumab would be compared to the ACT if the patients who discontinued therapy would had received a subsequent therapy. Due to these restrictions, the added benefit cannot be quantified. However, since it is not assumed that the large effects in individual AEs (especially paraesthesia) would be massively reduced by dose reductions, this non-quantifiable added benefit is at least “considerable”. Therefore, the overall consideration results in an indication of a non-quantifiable added benefit that is at least “considerable” for patients with at least 4 migraine days per month for whom conventional migraine prophylaxis is an option. Due to the described limitations, the result of the benefit assessment can only be transferred to the German health care context to a limited extent.

Table 3 shows a summary of probability and extent of the added benefit of erenumab.

Table 3: Erenumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis[b]	Metoprolol or propranolol or flunarizine or **topiramate** or amitriptyline or clostridium botulinum toxin type A under consideration of approval and prior therapy	Indication of a non-quantifiable added benefit (at least "considerable")

a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. This population was only a subpopulation of the approved therapeutic indication and comprised pretreated and treatment-naive patients. The subpopulation of patients who do not respond to any of the drug therapies/drug classes mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, Clostridium botulinum toxin type A), for whom these are not suitable or who cannot tolerate them, is not the subject of the present benefit assessment.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of erenumab in comparison with topiramate as ACT for the prophylaxis of migraine in patients who have at least 4 migraine days per month.

The specification of the ACT results in 2 subpopulations for the approved therapeutic indication of erenumab. Only the subpopulation of patients for whom conventional migraine prophylaxis is an option is relevant for the present assessment. The G-BA specified the ACT presented in Table 4 for this subpopulation. The subpopulation of patients who do not respond to any of the drug therapies/drug classes mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, Clostridium botulinum toxin type A), for whom these are not suitable or who cannot tolerate them, is not the subject of the present benefit assessment.

Table 4: Research question of the benefit assessment of erenumab

Therapeutic indication	**ACT**[a]
Adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis[b]	Metoprolol or propranolol or flunarizine or **topiramate** or amitriptyline or clostridium botulinum toxin type A under consideration of approval and prior therapy
a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. This population was only a subpopulation of the approved therapeutic indication and comprised pretreated and treatment-naive patients. The subpopulation of patients who do not respond to any of the drug therapies/drug classes mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, Clostridium botulinum toxin type A), for whom these are not suitable or who cannot tolerate them, is not the subject of the present benefit assessment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the specification of the ACT and chose topiramate from the cited options. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum treatment duration of 12 weeks were used for the derivation of the added benefit. This deviates from inclusion criteria of the company, which specified a minimum study duration of 24 weeks.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on erenumab (status: 8 February 2021)
- bibliographical literature search on erenumab (last search on 3 February 2021)
- search in trial registries/trial results databases for studies on erenumab (last search on 3 February 2021)
- search on the G-BA website for erenumab (last search on 15 February 2021)

To check the completeness of the study pool:

- search in trial registries for studies on erenumab (last search on 12 May 2021); for search strategies, see Appendix C of the full dossier assessment

Besides the HER-MES study, the study CAMG334A2401 [3,4] was identified from the check. CAMG334A2401 is an RTC that included adult patients with at least 4, but less than 15 migraine days per month and 1 or 2 prior failed migraine prophylaxis. The patients received either erenumab or another locally approved migraine prophylaxis for a period of 52 weeks. According to the registry entry and the information provided by the company, the study is ongoing and results are not available yet [3]. The study is expected to end in October 2022. Therefore, the study was not considered further for the present benefit assessment.

2.3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: erenumab vs. topiramate

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
CAMG334ADE01 (HER-MES[d])	No	Yes	No	Yes [5]	Yes [6,7]	No

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment of erenumab in comparison with the ACT consists of the study HER-MES and corresponds to the study pool of the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: erenumab vs. topiramate

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
HER-MES	RCT, double-blind, parallel	Adult[b] patients with an average of ≥ 4 migraine days/months over the last 3 months, who were either ▪ treatment-naive or ▪ had not responded to up to 3 of the following migraine prophylaxes[c], or for whom these drugs were not suitable[d]. metoprolol/propranolol, amitriptyline or flunarizine	Erenumab (N = 389) topiramate (N = 388)	▪ Screening: 0-2 weeks ▪ baseline period[e]: 4 weeks ▪ treatment: 24 weeks ▪ observation period: 4-8 weeks[f]	79 centres in Germany 02/2019–07/2020	Primary: discontinuation of treatment due to AEs secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Age from ≥ 18 and ≤ 65 years at the time of screening, at the onset of the migraine ≤ 50 years.
c. Treatment failure due to lack of efficacy (no significant reduction in headache frequency after administration of the corresponding medication for a reasonable period [the therapy guidelines of the European Headache Federation recommend at least 2 to 3 months] at generally accepted doses based on the physician's assessment within the last 5 years prior to screening) or due to poor tolerability (documented discontinuation of the corresponding medication due to adverse events at any time prior to screening).
d. The patient is not considered suitable for the therapy due to medical reasons, such reasons may be contraindications or precautions in the local label, national guidelines or other locally binding documents (confirmed by the treating physician).
e. Within the baseline phase, the inclusion criterion "migraine frequency (≥ 4 migraine days/month)" and the compliance in completing the electronic migraine diary (≥ 80%) were checked.
f. Patients who discontinued the study prematurely were invited to a follow-up visit 8 weeks after the last dose. Patients who completed the study were invited to a follow-up visit 4 weeks after the last dose. Patients who discontinued treatment were subject to further observation.

AE: adverse event; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: erenumab vs. topiramate

Study	Intervention	Comparison
HER-MES	Erenumab 70 mg or 140 mg[a], SC, every 4 weeks + Placebo orally twice daily	Topiramate 50-100 mg[b] orally, twice daily + placebo: SC every 4 weeks **Titration phase (6 weeks)** ▪ week 1: 25 mg once daily, in the evening ▪ from week 2: weekly increase by 25 mg up to the highest tolerable dose[c] **maintenance phase: (18 weeks)** ▪ with the highest tolerable dose (50 mg, 75 mg or 100 mg) **tapering[d] (1 week)** ▪ after visit 199 1-week reduction of the daily dose by 50 mg
	No dose reductions allowed	
	Permitted pretreatment ▪ metoprolol/propranolol, amitriptyline, flunarizine (not within 5 half-lives before the start of or during the baseline phase) ▪ constant non-pharmacological therapies within the last 3 months before baseline **non-permitted pretreatment** ▪ topiramate, valproate, botulinum toxin type A ▪ within 1 month before or during the baseline phase: ▫ medical device or other treatment for migraine prophylaxis ▫ opioid-containing or butalbitate-containing analgesics ≥ 4 days per month **permitted concomitant treatment** ▪ drug and non-drug treatment for the treatment of acute migraine attacks	

a. In case of inadequate response, the dose could be increased from 70 mg to 140 mg. Dose reduction from 140 mg to 70 mg was not allowed.
b. Highest tolerable dose that was reached in the titration phase (see maintenance phase).
c. Individual patients could maintain a dose for longer than one week if deemed necessary. In the study, the aim was for patients to reach the dose of 100 mg recommended by the SPC by titrating up the topiramate dose. Only if this was deemed impossible for safety reasons could the patient start the maintenance phase with a lower dose to avoid side effects.
d. Only for patients taking a daily dose of 75 mg or 100 mg.

CGRP: calcitonin gene-related peptide; RCT: randomized controlled trial

Study design

The HER-MES studies is a randomized, double-blind study that compares erenumab with topiramate. The study included adult patients with at least 4 migraine days per month in at least 2 different migraine attacks, who were either treatment-naive or had not responded to up to 3 of the following migraine prophylaxes, or for whom these drugs were not suitable: metoprolol/propranolol, amitriptyline or flunarizine.

A total of 777 patients were randomly allocated in a 1:1 ratio to treatment either with erenumab (N = 389) or with topiramate (N = 388). Randomization was stratified by number of migraine days per month (from 4 to 7/8 up to 14/≥ 15). The study was only conducted in German study centres.

In the HER-MES study, patients received the highest individually tolerated dose of erenumab or topiramate. In the erenumab arm, patients received 70 mg or 140 mg erenumab every 4 weeks over a 24-week period. In the topiramate arm, patients received 50 mg to 100 mg topiramate over an 18-week period after a 6-week titration phase. The patients also received matching placebo preparations in both study arms. In the topiramate arm, it was possible to extend the dose titration or to reduce the target dose if AEs occurred. However, the dose of topiramate (and erenumab) once reached was not allowed to be reduced again during the study. No restrictions on dose reductions are defined in the respective SPC, so that these are potentially possible [8,9]. The non-permitted dose reduction in the HER-MES study thus restricted the investigator's options in the event of AEs and might thus have influenced the rate of discontinuations due to AEs.

After premature discontinuation of treatment, patients were to remain in the study and complete their migraine diary. However, intake of other migraine prophylaxes as subsequent therapy was not allowed. The company stated that patients in the topiramate arm most frequently discontinued treatment during the first 6 weeks. Consequently, those patients who discontinued treatment received no migraine prophylaxis over a prolonged period in the study. Patients were only allowed to continue their therapies for the treatment of acute migraine attacks.

In summary, it is unclear whether and to what extent the prohibited dose reduction influenced the AEs and the discontinuation rates in the study. In addition to the outcomes mentioned, it is also unclear for the other outcomes how large the influence on the corresponding effects of erenumab would be compared to the ACT if the patients who discontinued therapy would had received a subsequent therapy. This uncertainty was taken into account in the interpretation of the study results.

In the erenumab arm, patients were treated 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.

Primary outcome of the study was “discontinuations due to AEs”. Patient-relevant secondary outcomes were all-cause mortality and outcomes of the categories of morbidity, health-related quality of life AEs.

Characteristics of the study population

Table 8 shows the characteristics of the patients in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: erenumab vs. topiramate

Study characteristic category	Erenumab N[a] = 389	Topiramate N[a] = 388
HER-MES		
Age [years], mean (SD)	41 (12.4)	41 (12.4)
Sex [F/M], %	85/15	86/14
Family origin, n (%)		
Caucasian	383 (98.7)	387 (99.7)
Black	0 (0)	0 (0)
Asian	1 (0.3)	0 (0)
Unknown	1 (0.3)	0 (0)
Other	3 (0.8)	1 (0.3)
Age at first occurrence of migraine [years], mean (SD)	18.9 (9.6)	18.8 (9.3)
Number of migraine days [days/months]		
Mean (SD)	10.3 (4.0)	10.5 (3.8)
< 4, n (%)	2 (0.5)	0 (0)
4-7, n (%)	94 (24.2)	92 (23.7)
8-14, n (%)	248 (63.9)	254 (65.5)
≥ 15, n (%)	43 (11.1)	42 (10.8)
Unknown, n (%)	1 (0.3)	0 (0)
General impairment from headache, measured with the HIT-6, mean (SD)	63.7 (4.2)	63.9 (4.0)
Number of headache days [days/months], mean (SD)	11.4 (4.2)	11.5 (4.1)
Acute headache medication, n (%)		
None	10 (2.6)	10 (2.6)
Any acute medication	378 (97.4)	378 (97.4)
Migraine-specific	304 (78.4)	320 (82.5)
Not migraine-specific	74 (19.1)	58 (14.9)
Failed drug migraine prophylaxis[c], n (%)		
Any	156 (40.2)	159 (41.0)
1 failed	115 (29.6)	123 (31.7)
2 failed	37 (9.5)	31 (8.0)
3 failed	4 (1.0)	5 (1.3)
Any non-drug prophylaxis of migraine, n (%)	ND	ND
Treatment discontinuation[b], n (%)	55 (14.1)	157 (40.5)
Study discontinuation, n (%)	16 (4.1)	22 (5.7)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. The main reason for treatment discontinuation was the occurrence of AEs (erenumab: 76%, topiramate: 96%)

F: female; HIT-6: Headache Impact Test-6; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients were largely balanced between the two study arms. Almost all patients were of Caucasian origin; the mean age was 41 years. The proportion of women was 86% and thus higher than the proportion of men.

Patients had an average of 10 migraine days per month. Approx. 60% of the patients had no drug migraine prophylaxis before the start of the study and were thus treatment-naive. In the remaining patients, at least 1 migraine prophylaxis had failed before.

The proportion of patients who discontinued their treatment prematurely was 40% in the topiramate arm and thus clearly higher than in the erenumab arm (14%). In both study arms, the main reason for treatment discontinuation were AEs.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: erenumab vs. topiramate

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
HER-MES	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the results of the HER-MES study was rated as low. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms, measured with migraine days/month
  - general impairment from headache, recorded using the HIT-6
- Health-related quality of life

- measured using the Short Form 36 – version 2 Health Survey (SF-36v2)

- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: erenumab vs. topiramate:

Study	Outcomes										
	All-cause mortality	Symptoms (migraine days/month)	General impairment from headache (HIT-6)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Nervous system disorders (SOC, AEs)[a]	Nausea (PT, AEs)	Constipation (PT, AEs)	Fatigue (PT, AEs)	Decreased appetite (PT, AEs)
HER-MES	Yes[b]	Yes	Yes[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Including: paraesthesia (PT, AEs), disturbance in attention (PT, AEs) and dizziness (PT, AEs).
b. Determined by recording of AEs.
c. The company assigned the outcome recorded via the HIT-6 instrument to "health-related quality of life".

AE: adverse event; HIT-6: Headache Impact Test-6; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class

Symptoms - migraine days/month

In the following benefit assessment, the outcome "symptoms" was assessed on the basis of the migraine days/month. In the HER-MES study, a migraine day was defined as a calendar day on which the patient had migraine headaches, regardless of whether the pain starts, continues or recurs on that day. Migraine headache is defined as follows: migraine with or without aura of at least 30 minutes duration that meets at least 1 of the following two criteria:

1) At least 2 of the following headache characteristics:
   - one-sided
   - throbbing
   - moderate to severe
   - aggravated by exertion/physical activity
2) At least 1 of the following concomitant symptoms:
   - nausea and/or vomiting
   - photophobia and phonophobia

If a migraine-specific acute medication is taken during an aura or for the treatment of the headache, this day is counted as a migraine day - regardless of the duration and type of pain or concomitant symptoms.

In its dossier, the company presented several analyses for the outcome "symptoms (migraine days/month)":

- Analysis of the change in the number of migraine days/month between start of the study and month 1
- Analysis of the change in the number of migraine days/month between start of the study and the last 3 months
- Analyses of the proportions of patients with a reduction of the migraine days/month by ≥ 50% over the first month (responder analyses)
- Analyses of the proportions of patients with a reduction of the migraine days/month by ≥ 50% over the last 3 months (responder analyses)

The responder analyses on the reduction of the migraine days/month by ≥ 50% are relevant for the benefit assessment. The population considered in the present benefit assessment consists of patients with at least 4 migraine days/month for whom conventional migraine prophylaxis is an option. Against the background of the patients' symptom burden, reduction by ≥ 50% already represents an appropriate response criterion. The responder analyses for both periods of time were included in the present benefit assessment.

General impairment from headache (HIT-6)

HIT-6 is a validated instrument for the recording of a patient's headache-related impairment within the past month [10-12].

The company assigned the HIT-6 to "health-related quality of life". This view is not shared. As described in the first benefit assessment of erenumab, it is not comprehensible that the HIT-6 instrument reflects the dimensions of health-related quality of life (at least the physical,

psychological and social ones) [13]. For this reason, the instrument was assigned to the outcome category "morbidity".

In its dossier, the company presented several analyses for HIT-6.

- analysis of the change in the total score of the HIT-6 instrument between start of the study and week 24
- analyses of the proportions of patients with an improvement by ≥ 5 points (responder analyses)
- analyses of the proportions of patients with an improvement by ≥ 6.3 points (responder analyses)

As explained in the *General Methods* of the Institute [1,14], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). The responder analyses on the improvement by ≥ 6.3 points correspond to these criteria with the present scale range of 42 points for the HIT-6 and are therefore used for the present benefit assessment.

The company presented the responder analyses on the improvement by ≥ 5 points as supplementary information in Appendix A of the full dossier assessment, because this response criterion was used in earlier assessments in the therapeutic indication of migraine [13].

Health-related quality of life (SF-36v2)

The SF-36 is a generic, validated questionnaire for patients' self-assessment of health-related quality of life [15].

In its dossier, the company presented several analyses for SF.36v2.

- Analysis of the change in the PCS/MCS sum score between start of the study and week 24
- Analyses of the proportions of patients with an improvement by ≥ 5 points (responder analyses)
- Analyses of the proportions of patients with an improvement by ≥ 9.4 points or 9.6 points (responder analyses)
- Analyses of the proportions of patients with an improvement by ≥ 11.2 points or 12.5 points (responder analyses)

For the recording of health-related quality of life using the SF-36, it should be noted that the company determined the response threshold of 15% of the scale range for the normalized values of the sum scores (MCS and PCS) in 2 different ways, which it referred to as "scale in practice" and "theoretical" response scale. The response threshold for the “scale in practice” calculated

by the company leads to response thresholds of 9.6 points for the MCS and 9.4 points for the PCS. The approach is consistent with the approach described in dossier assessment A20-90 [16] taking into account the observed values of a norm sample from 2009. The analyses presented by the company were therefore relevant for the present assessment and were used. The approach according to the "theoretical" response threshold arrived at deviating response thresholds of 12.5 points for the MCS and 11.2 points for the PCS and, as described in A20-90, is based on minimizing and maximizing the PCS and MCS on the basis of the 2009 norm sample. A detailed explanation of this can be found in dossier assessment A20-90 [16] .

The responder analyses used by the company for the improvement by ≥ 5 points and by ≥ 11.2 or 12.5 points as well as the analyses on the changes from baseline were not used for the dossier assessment. The responder analysis on the improvement by ≥ 5 points are presented as supplementary information in Appendix A.

2.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: erenumab vs. topiramate

Study		Outcomes										
	Study level	All-cause mortality	Symptoms (migraine days/month)	General impairment from headache (HIT-6)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Nervous system disorders (SOC, AEs)[a]	Nausea (PT, AEs)	Constipation (PT, AEs)	Fatigue (PT, AEs)	Decreased appetite (PT, AEs)
HER-MES	N	N	N	N	N	N	N	N	N	N	N	N

a. Including: paraesthesia (PT, AE), disturbance in attention (PT, AE) and dizziness (PT, AE)

AE: adverse event; H: high; HIT-6: Headache Impact Test-6; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class

The company assessed the risk of bias as low for each of the results of the outcomes included in the present benefit assessment. The assessment of the risk of bias was accepted.

Transferability of the study results to the German health care context

In everyday practice, patient adherence to migraine prophylaxis is low [17]. Many patients discontinue their treatments due to AEs or lack of efficacy. However, training of patients on

dose adjustments and therapy expectations as well as patient involvement in treatment decisions could improve the adherence.

Also in the HER-MES study, the discontinuation rate was high, in particular in the topiramate arm, where 40% of the patients discontinued treatment prematurely. AEs were the main reason for discontinuation of therapy in both study arms (erenumab: 76%, topiramate: 96%). This reflects everyday practice. However, the high discontinuation rates may also be due to the study design. In everyday practice, patients who discontinue a prophylactic treatment also have the option of a subsequent therapy. However, in the HER-MES study, no prophylactic follow-up therapy was allowed after discontinuation of treatment. As described in Section 2.3.2, the comparison of erenumab with the ACT is potentially influenced by the lack of an option for dose reduction option in case of AEs and the lack of subsequent therapy after premature discontinuation of the study medication. Therefore, the result of the benefit assessment can only be transferred to the German health care context to a limited extent.

From the point of view of the company, the results on the population relevant to the assessment are transferable to the German healthcare context, as the target population presented in the dossier is structurally identical to the migraine population in Germany with regard to demographic and other characteristics, diagnosis and concomitant therapy.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4.3 Results

Table 12 summarizes the results of the comparison of erenumab with topiramate in patients with at least 4 migraine days per month who are candidates for conventional migraine prophylaxis. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The results of the outcome "general impairment from headache (HIT-6)", operationalized using an improvement by ≥ 5 points, are presented as supplementary information in Appendix A. Tables on common AEs, SAEs and discontinuations due to AEs can be found in Appendix B of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: erenumab vs. topiramate (multipage table)

Study outcome category outcome	Erenumab		Topiramate		Erenumab vs. topiramate
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
HER-MES					
Mortality					
All-cause mortality	388	0 (0)	388	0 (0)	–
Morbidity					
Symptoms: migraine days/month					
Reduction by ≥ 50% over the last 3 months	388[b]	215 (55.4)	388[b]	121 (31.2)	1.78 [1.50; 2.11]; < 0.001
Reduction by ≥ 50% over the last 1 month	388[c]	147 (37.9)	388[c]	86 (22.2)	1.71 [1.36; 2.14]; < 0.001
General impairment from headache (HIT-6)[d]	388[e]	251 (64.7)	388[e]	178 (45.9)	1.41 [1.24; 1.61]; < 0.001
Health-related quality of life					
SF-36v2[f]					
Physical Component Summary (PCS)[g]	388[h]	93 (24.0)	388[h]	77 (19.8)	1.21 [0.92; 1.58]; 0.166
Mental Component Summary (MCS)[i]	388[h]	45 (11.6)	388[h]	31 (8.0)	1.45 [0.94; 2.24]; 0.093
Side effects					
AEs (supplementary information)	388	338 (87.1)	388	361 (93.0)	–
SAEs	388	10 (2.6)	388	19 (4.9)	0.53 [0.25; 1.12]; 0.095
Discontinuation due to AEs	388	41 (10.6)	388	151 (38.9)	0.27 [0.20; 0.37]; < 0.001
Nervous system disorders (SOC, AE), including:	388	96 (24.7)	388	253 (65.2)	0.38 [0.31; 0.46]; < 0.001
Paraesthesia (PT, AE)	388	17 (4.4)	388	159 (41.0)	0.11 [0.07; 0.17]; < 0.001
Disturbance in attention (PT, AE)	388	18 (4.6)	388	63 (16.2)	0.29 [0.17; 0.47]; < 0.001
Dizziness (PT, AE)	388	28 (7.2)	388	60 (15.5)	0.47 [0.30; 0.71]; < 0.001
Nausea (PT, AE)	388	36 (9.3)	388	71 (18.3)	0.51 [0.35; 0.74]; < 0.001
Constipation (PT, AE)	388	48 (12.4)	388	12 (3.1)	4.00 [2.16; 7.41]; < 0.001
Fatigue (PT, AE)	388	44 (11.3)	388	74 (19.1)	0.59 [0.42; 0.84]; 0.003
Decreased appetite (PT, AE)	388	8 (2.1)	388	40 (10.3)	0.20 [0.09; 0.42]; < 0.001

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: erenumab vs. topiramate (multipage table)

Study outcome category outcome	Erenumab		Topiramate		Erenumab vs. topiramate
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
a. Wald test. b. The values of 10 (2.6%) patients in the erenumab arm and 17 (4.4%) patients in the topiramate arm were imputed using non-responder imputation. c. The values of 5 (1.3%) patients in the erenumab arm and 3 (0.8%) patients in the topiramate arm were imputed using non-responder imputation. d. Patients with improvement of ≥ 6.3 points (corresponds to 15% of the scale range). e. The values of 24 (6.2%) patients in the erenumab arm and 30 (7.7%) patients in the topiramate arm were imputed using non-responder imputation. f. Information on subscales were not available. g. Patients with improvement by ≥ 9.4 points (corresponds to 15% of the scale range). h. The values of 25 (6.4%) patients in the erenumab arm and 33 (8.5%) patients in the topiramate arm were imputed using non-responder imputation. i. Patients with improvement by ≥ 9.6 points (corresponds to 15% of the scale range). AE: adverse event; CI: confidence interval; HIT-6: Headache Impact Test-6; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; PCS: Physical Component Summary; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class					

Based on the available information, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

No deaths occurred in the course of the study. There was no hint of an added benefit of erenumab in comparison with topiramate for the outcome "all-cause mortality"; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Symptoms (migraine days/month)

Responder analyses on a reduction by ≥ 50% over the last 3 months and over the first month are used for the outcome "symptoms" (migraine days/month).

There is a statistically significant difference in favour of erenumab versus topiramate both for the period of the last 3 months and for the period of the first month. This resulted in an indication of an added benefit of erenumab in comparison with topiramate for the outcome "symptoms (migraine days/month)".

This concurs with the company's assessment. For this outcome, however, the company additionally used analyses on the change from baseline for the derivation of the added benefit.

General impairment from headache (HIT-6)

Responder analyses on the improvement by ≥ 6.3 points were used for the outcome "general impairment from headache (HIT-6)".

A statistically significant difference was shown in favour of erenumab versus topiramate. This resulted in an indication of an added benefit of erenumab in comparison with topiramate for the outcome "general impairment from headache (HIT-6)".

This deviates from the approach of the company insofar as the company assigned the HIT-6 to "health-related quality of life". Moreover, the company additionally used analyses on the change from baseline and responder analyses on the improvement by ≥ 5 points and derived an added benefit on this basis.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

For the outcome "health-related quality of life (SF-36v2)", responder analyses on improvement by ≥ 9.4 points are used for the PCS, and responder analyses on improvement by ≥ 9.6 points are used for the MCS.

A statistically significant difference between the treatment groups was neither found for the PCS nor for the MCS. There was no hint of an added benefit of erenumab in comparison with topiramate for the outcome "health-related quality of life (SF-36v2)"; an added benefit is therefore not proven.

This deviates from the assessment of the company, which additionally used analyses on the change from baseline and responder analyses on the improvement by ≥ 5 points and derived an added benefit on this basis.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from erenumab in comparison with topiramate; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

A statistically significant difference in favour of erenumab was shown for the outcome "discontinuation due to AEs". This resulted in an indication of lesser harm from erenumab in comparison with topiramate.

This concurs with the company's assessment.

Specific AEs

Nervous system disorders (including: paraesthesia, disturbance in attention, dizziness), nausea, fatigue, decreased appetite

There was a statistically significant difference in favour of erenumab for the outcome "nervous system disorders" and the events "paraesthesia", "disturbance in attention" and "dizziness" included therein, as well as for the outcomes "nausea", "fatigue" and "decreased appetite". This resulted in an indication of lesser harm from erenumab versus topiramate for the outcome "nervous system disorders" and the events "paraesthesia", "disturbance in attention" and "dizziness" included therein, as well as for each of the outcomes "nausea", "fatigue" and "decreased appetite".

This deviates from the assessment of the company, which derived an added benefit on the basis of all AEs and did not consider individual events.

Constipation

A statistically significant difference to the disadvantage of erenumab was shown for the outcome "constipation". For the outcome "constipation", this resulted in an indication of greater harm from erenumab in comparison with topiramate.

This deviates from the assessment of the company, which derived an added benefit on the basis of all AEs and did not consider individual events.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- sex (male/female)
- migraine days/month (4-7/8-14/≥ 15)

Only the outcome "discontinuation due to AEs" was predefined for the corresponding subgroup analyses. However, the company presented subgroup analyses on the two characteristics mentioned above for all outcomes considered.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

For the cases with at least one zero cell in a subgroup, the company stated that an interaction test was not possible. Deviating from this, a test on the level of aggregate data (Q-test) was carried out in both study arms in the Institute's calculation using a correction term of 0.5 in the case of subgroups with a zero cell.

No effect modifications result from the subgroup analyses.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

As described in Section 2.3.2, the comparison of erenumab with the ACT is potentially influenced by the lack of an option for dose reduction option in case of AEs and the lack of subsequent therapy after premature discontinuation of the study medication. Due to these restrictions in the application of the therapy, the added benefit is not quantifiable in the overall assessment. Based on the results presented in Section 2.4, the extent of the respective added benefit is additionally assessed at outcome level (see Table 13) in the following, but the extent of the added benefit is not quantified for the overall conclusion.

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification for these outcomes is justified.

Symptoms (migraine days/month)

The outcome "symptoms" (migraine days/month) was allocated to the outcome category "serious/severe symptoms/late complications". This is largely derived from the available baseline values of the study population on "general impairment from headache (HIT-6)". The values show that the patients in the HER-MES study had very severe impairment from headache at the start of the study (see Table 8). Although the HIT-6 instrument is used to assess headache in general and not specifically migraine headache, the present benefit assessment is based on the assumption that the burden of disease from migraine headache makes HIT-6 suitable for assessing the outcome category for the outcome "symptoms (migraine days/month"). Patients also had an average of 10 migraine days per month or 11 headache days per month at baseline, and almost all patients were taking acute headache medication. In the overall consideration, the outcome was therefore assigned to the outcome category "serious/severe symptoms/late complications".

This assessment on the outcome category deviates from that of the company, which did not assign this outcome to any outcome category.

General impairment from headache (HIT-6)

The outcome “general impairment from headache (HIT-6)” is assigned to the outcome category “serious/severe symptoms/late complications”. For reasons, see the arguments for the classification of the outcome category of the outcome “symptoms (migraine days/month)”. This deviates from the assessment of the company, which assigned this outcome to “health-related quality of life”.

Side effects

The outcome "discontinuation due to AEs" only includes a few events that were classified as serious. In addition, the company classified the AEs into severe and non-severe AEs, but did not provide an explanation for this classification. Therefore, the outcome “discontinuation due to AEs” was assigned to the category of non-serious/non-severe side effects.

For the outcomes on specific AEs (nervous system disorders, nausea, constipation, fatigue, decreased appetite), it is not clear whether the events were serious. Moreover, as with the outcome “discontinuation due to AEs”, the company did not provide an explanation for the classification into severe and non-severe events. The outcomes were therefore assigned to the category “non-serious/non-severe side effects”.

This assessment on the outcome category deviates from that of the company, which did not assign these AEs to any outcome category.

Table 13: Extent of added benefit at outcome level: erenumab vs. topiramate (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Erenumab vs. topiramate** **proportion of events (%)** **RR [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Symptoms: migraine days/month		
Reduction by ≥ 50% over the last 3 months	55.4% vs. 31.2% 1.78 [1.50; 2.11] 0.56 [0.47; 0.67][c] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% added benefit, extent: "major"
Reduction by ≥ 50% over the first month	37.9% vs. 22.2% 1.71 [1.36; 2.14] 0.59 [0.47; 0.73][c] p < 0.001 probability: "indication"	
General impairment from headache (HIT-6); improvement by ≥ 6.3 points	64.7% vs. 45.9% 1.41 [1.24; 1.61] 0.71 [0.62; 0.81][c] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications 0.75 ≤ CI_u < 0.90 added benefit, extent: "considerable"
Health-related quality of life		
SF-36v2		
Physical Component Summary (PCS)	24.0% vs. 19.8% 1.21 [0.92; 1.58] p = 0.166	Lesser benefit/added benefit not proven
Mental Component Summary (MCS)	11.6% vs. 8.0% 1.45 [0.94; 2.24] p = 0.093	Lesser benefit/added benefit not proven
Side effects		
SAEs	2.6% vs. 4.9% 0.53 [0.25; 1.12] p = 0.095	Greater/lesser harm not proven
Discontinuation due to AEs	10.6% vs. 38.9% 0.27 [0.20; 0.37] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

Table 13: Extent of added benefit at outcome level: erenumab vs. topiramate (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Erenumab vs. topiramate** **proportion of events (%)** **RR [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Nervous system disorders (SOC, AE), including:	24.7% vs. 65.2% 0.38 [0.31; 0.46] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Paraesthesia (PT, AEs)	4.4% vs. 41.0% 0.11 [0.07; 0.17] p < 0.001 probability: "indication"	
Disturbance in attention (PT, AEs)	4.6% vs. 16.2% 0.29 [0.17; 0.47] p < 0.001 probability: "indication"	
Dizziness (PT, AEs)	7.2% vs. 15.5% 0.47 [0.30; 0.71] p < 0.001 probability: "indication"	
Nausea (PT, AEs)	9.3% vs. 18.3% 0.51 [0.35; 0.74] p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Constipation (PT, AEs)	12.4% vs. 3.1% 4.00 [2.16; 7.41] 0.25 [0.13; 0.46][c] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Fatigue (PT, AEs)	11.3% vs. 19.1% 0.59 [0.42; 0.84] p = 0.003 probability: "indication"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Decreased appetite (PT, AEs)	2.1% vs. 10.3% 0.20 [0.09; 0.42] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"

Table 13: Extent of added benefit at outcome level: erenumab vs. topiramate (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Erenumab vs. topiramate** **proportion of events (%)** **RR [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; HIT-6: Headache Impact Test-6; MCS: Mental Component Summary; PCS: Physical Component Summary; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class		

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of erenumab in comparison with topiramate

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ symptoms (migraine days/month): indication of added benefit - extent: "major" ▪ general impairment from headache: indication of an added benefit, extent: "considerable"	–
Non-serious/non-severe side effects ▪ discontinuation due to AEs: indication of lesser harm – extent: "considerable" ▪ specific AEs: nervous system disorders (including: paraesthesia, disturbance in attention, dizziness), nausea, decreased appetite: Indication of lesser harm – extent: considerable ▪ specific AEs: fatigue: indication of lesser harm – extent: "minor"	Non-serious/non-severe side effects ▪ specific AEs: constipation: indication of greater harm – extent: "considerable"
AE: adverse event	

Overall, there are several positive effects and one negative effect. On the side of the positive effects, there are indications of major or considerable substantial added benefit of erenumab compared to topiramate for the serious/severe symptoms/late complications. Moreover, for the non-serious/not severe side effects, there are indications of lesser harm in several outcomes, the majority with the extent "considerable". In contrast, a negative effect with the extent "considerable" was shown for the non-serious/non-severe side effects.

As described in Section 2.3.2, it is unclear whether and to what extent the prohibited dose reduction influenced the AEs and the discontinuation rates in the study. In addition to the outcomes mentioned, it is also unclear for the other outcomes how large the influence on the corresponding effects of erenumab would be compared to the ACT if the patients who discontinued therapy would had received a subsequent therapy. Due to these restrictions, the added benefit cannot be quantified. However, since it is not assumed that the large effects in individual AEs (especially paraesthesia) would be massively reduced by dose reductions, this non-quantifiable added benefit is at least "considerable". Therefore, the overall consideration results in an indication of a non-quantifiable added benefit that is at least "considerable" for patients with at least 4 migraine days per month for whom conventional migraine prophylaxis is an option. Due to the described limitations, the result of the benefit assessment can only be transferred to the German health care context to a limited extent.

The result of the assessment of the added benefit of erenumab in comparison with the ACT is summarized in Table 15.

Table 15: Erenumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients who have at least 4 migraine days per month and who are candidates for conventional migraine prophylaxis[b]	Metoprolol or propranolol or flunarizine or **topiramate** or amitriptyline or clostridium botulinum toxin type A under consideration of approval and prior therapy	Indication of a non-quantifiable added benefit (at least "considerable").

a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. This population was only a subpopulation of the approved therapeutic indication and comprised pretreated and treatment-naive patients. The subpopulation of patients who do not respond to any of the drug therapies/drug classes mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, Clostridium botulinum toxin type A), for whom these are not suitable or who cannot tolerate them, is not the subject of the present benefit assessment.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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