IQWiG Reports – Commission No. A18-71

Erenumab (migraine) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Erenumab (Migräne) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 January 2019). Please note: This document was translated by an external translator and 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 October 2018.

Research question

The aim of this report was to assess the added benefit of erenumab in comparison with the appropriate comparator therapy (ACT) for migraine prevention in adult patients with at least 4 migraine days per month.

Table 2 presents the research questions of the benefit assessment and the ACT specified by the G-BA.

Table 2[2]: Research questions of the benefit assessment of erenumab

Research question	Indication	ACT[a]
Adult patients with at least 4 migraine days per month		
1	Untreated patients as well as patients who did not respond adequately to at least 1 prophylactic medication or did not tolerate it or are ineligible for it.	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline, each as approved and under consideration of prior therapy.
2	Patients who do not respond to the following therapies (drug classes), are ineligible for them, or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline[b]	Valproic acid[c] or *Clostridium botulinum* toxin type A[d]
3	Patients who do not respond to any of the following therapies (drug classes), are ineligible for them, or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid[c] or *Clostridium botulinum* toxin type A[d]	BSC[e]

a: Presentation of the respective ACT specified by the G-BA.
b: All 4 drug classes defined as the ACT for research question 1 (beta blockers, flunarizine, topiramate, or amitriptyline) must have been considered before the patients fall under research question 2. Both valproic acid and *Clostridium botulinum* toxin type A are not standard options for all patients.
c: In accordance with the G-BA Drug Prescribing Directive, Section K, Annex VI: if treatment with all other drugs approved for the indication was unsuccessful or is contraindicated.
d: Only for chronic migraine in accordance with approval.
e: BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

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

To simplify presentation and improve readability, the running text of this benefit assessment uses the following terms for the research questions:

- Research question 1: adult patients eligible for treatment with metoprolol or propranolol or flunarizine or topiramate or amitriptyline
- Research question 2: adult patients eligible for treatment with valproic acid or *Clostridium botulinum* toxin type A
- Research question 3: adult patients for whom best supportive care (BSC) is the only remaining treatment option

The company followed the G-BA's specification of the ACT.

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 deriving any added benefit.

Results

Research question 1: Adult patients eligible for treatment with metoprolol or propranolol or flunarizine or topiramate or amitriptyline

The company did not present any data for assessing the added benefit of erenumab in adult patients eligible for treatment with metoprolol or propranolol or flunarizine or topiramate or amitriptyline. An added benefit of erenumab in comparison with the ACT is therefore not proven for these patients.

Research question 2: Adult patients eligible for treatment with valproic acid or Clostridium botulinum toxin type A

The company did not present any data for assessing the added benefit of erenumab in adult patients eligible for treatment with valproic acid or *Clostridium botulinum* toxin type A. An added benefit of erenumab in comparison with the ACT is therefore not proven for these patients.

Research question 3: Adult patients for whom best supportive care (BSC) is the only remaining treatment option

The LIBERTY study was included for assessing the added benefit of erenumab in adult patients for whom best supportive care (BSC) is the only remaining treatment option.

Study design

The LIBERTY study is a randomized, double-blind, parallel-group study comparing erenumab + BSC with placebo + BSC over the course of 12 weeks in adult patients with episodic migraine documented for at least 12 months. Within the most recent 3 months, patients had to have had on average 4 to 14 migraine days per month (mean of 9.1 migraine days per month), have been treated unsuccessfully with 2 to 4 prior drug-based migraine prophylactic treatments, and have

failed to respond to or been ineligible for valproic acid therapy. Overall, 246 patients were randomly allocated to treatment with erenumab (N = 121) or placebo (N = 125).

Patients received subcutaneous administration of 140 mg erenumab or placebo every 4 weeks. This dose is among the approved doses for erenumab. Patients additionally received BSC.

The primary outcome of the study was the percentage of patients with a ≥ 50% response in the reduction of monthly migraine days up to Week 12. Relevant secondary outcomes were symptoms, further outcomes on morbidity, and outcomes on adverse events (AEs).

For the benefit assessment, the company presented a subpopulation of the LIBERTY study for research question 3. It included patients who had received at least 2 of the following prior therapies (drug classes): propranolol/metoprolol, flunarizine, topiramate, or amitriptyline. Further, the subpopulation included by the company included only patients with prior valproic acid treatment and for whom valproic acid was the most recent treatment before study inclusion. This is due to the fact that, according to the G-BA Drug Prescribing Directive (Annex VI of Section K), valproic acid cannot be prescribed for migraine prophylaxis in adults unless "treatment with other approved drugs was unsuccessful or is contraindicated". The subpopulation presented by the company is considered suitable for answering research question 3. The LIBERTY study's subpopulation relevant for this benefit assessment comprises a total of 193 randomized patients.

For research question 3, the LIBERTY study provides data only on patients with 4 to 14 headache days per month, but not on patients who have chronic migraine as per the International Classification of Headache Disorders, 3rd Edition (ICHD-3). The latter defines chronic migraine as headache on more than 15 days a month for a period of more than 3 months, with the headache meeting migraine criteria on at least 8 days. This chronic migraine is also an indication for erenumab.

Risk of bias

The risk of bias on the study level was rated as low for the LIBERTY study.

The risk of bias of the outcomes of all-cause mortality, general headache burden (Headache Impact Test-6 [HIT-6]), health status (visual analogue scale [VAS] of the European Quality of Life Questionnaire 5 Dimensions [EQ-5D]) as well as the harm outcomes of serious AEs (SAEs) and discontinuation due to AEs is rated as low.

For the outcomes of symptoms (migraine days/month), physical functioning (Migraine Physical Function Impact Diary [MPFID]), and impairment of work productivity and activity (Work Productivity and Activity Impairment [WPAI]-Headache), the risk of bias is rated as high. For these outcomes, it is unclear whether a relevant number of days or relevant periods during the follow-up phase remained ignored.

On the basis of the available data, it is possible to derive at most indications, e.g. of an added benefit.

Mortality

All-cause mortality

In the LIBERTY study, no death occurred in either study arm. For the outcome of all-cause mortality, no statistically significant difference between treatment groups was therefore found. Consequently, there is no hint of an added benefit of erenumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Morbidity

Symptoms (migraine days/month)

For the outcome of migraine days/month, responder analyses were used regarding a reduction by ≥ 50%. There was a statistically significant difference in favour of erenumab + BSC. This difference also manifested in the outcome of migraine attacks/month, which was presented as supplementary information. For the outcome of migraine days/month, this results in a hint of added benefit of erenumab + BSC in comparison with BSC.

General headache burden (HIT-6)

For the outcome of general headache burden (HIT-6), responder analyses were used regarding an improvement by ≥ 5 points. There was a statistically significant difference in favour of erenumab + BSC. For this outcome, this results in an indication of added benefit of erenumab + BSC in comparison with BSC.

Physical functioning (MPFID)

For the outcome of physical functioning (MPFID) in the domains of impact on daily activities and physical functioning as well as the overarching question regarding overall impact on daily activities, the mean change showed a statistically significant effect in favour of erenumab + BSC. To check the relevance of the statistically significant results, the standardized mean difference (SMD) in the form of Hedges' g was considered in each case. However, the 95% confidence interval (CI) of the SMD (Hedges' g) does not fully lie outside of the irrelevance range of –0.2 to 0.2. Hence, it cannot be concluded that any of these effects are relevant. For the outcome of physical functioning (MPFID), there was therefore no hint of an added benefit of erenumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status (EQ-5D VAS), no statistically significant difference between treatment groups was found for mean change. Consequently, there is no hint of an added benefit of erenumab + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

Work productivity and activity impairment (WPAI headache)

For the outcome of work productivity and activity impairment (WPAI-Headache), the absenteeism score shows no statistically significant difference between treatment groups. For the scores of presenteeism, overall productivity loss (absenteeism + presenteeism), and activity impairment, a statistically significant effect in favour of erenumab + BSC was found. To check the relevance of the statistically significant results, the SMD in the form of Hedges' g was examined in each case. In this analysis, the 95% CI of SMD for the scores of presenteeism and overall productivity loss (absenteeism + presenteeism) did not lie completely outside the irrelevance range of −0.2 to 0.2. Hence, it cannot be concluded that any of these effects are relevant. For the activity impairment score, the 95% CI of SMD is completely below the irrelevance threshold of −0.2. This has been interpreted as a relevant effect. For activity impairment (WPAI), this results in a hint of an added benefit of erenumab + BSC in comparison with BSC. For absenteeism, presenteeism, or overall productivity loss (absenteeism + presenteeism), as measured by the WPAI, this does not result in a hint of added benefit of erenumab + BSC in comparison with BSC; an added benefit is therefore not proven for any of them.

Health-related quality of life

Health-related quality of life was not surveyed in the LIBERTY study.

Adverse events

SAEs and discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, no statistically significant difference between treatment groups was found. For each of these outcomes, there is therefore no hint of greater or lesser harm from erenumab + BSC in comparison with BSC. Greater or lesser harm is therefore not proven for these outcomes.

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

On the basis of the results presented, the probability and extent of added benefit of the drug erenumab in comparison with the ACT is assessed as follows:

Research questions 1 and 2

No data are available for assessing any added benefit for research question 1 (adult patients eligible for treatment with metoprolol or propranolol or flunarizine or topiramate or

[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].

amitriptyline) or research question 2 (adult patients eligible for treatment with valproic acid or *Clostridium botulinum* toxin type A). Consequently, an added benefit of erenumab in comparison with the ACT is not proven for these patients.

Research question 3

All things considered, on the basis of the LIBERTY study, only positive effects were found for adult patients with at least 4 migraine days/month for whom BSC is the only remaining treatment option. They were each observed in the outcome category of morbidity.

In summary, for adult patients with at least 4 migraine days/month for whom BSC is the only remaining treatment option, there is an indication of considerable added benefit of erenumab in comparison with BSC.

Adults with chronic migraine according to ICHD-3 who are also indicated for treatment with erenumab were not included in the LIBERTY study. On the basis of the results of the LIBERTY study, it seems unjustified to restrict the conclusion on added benefit to patients with episodic migraine in this benefit assessment. However, it is unclear whether the results of the LIBERTY study translate to patients with chronic migraine as defined by the above-stated criteria for whom BSC is the only remaining treatment option.

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

Table 3: Erenumab – probability and extent of added benefit

Research question	**Indication**	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with at least 4 migraine days per month			
1	Untreated patients as well as patients who did not respond adequately to at least 1 prophylactic medication or did not tolerate it or are ineligible for it.	Metoprolol or propranolol or flunarizine or topiramate or amitriptyline, each as approved and under consideration of prior therapy.	Added benefit not proven
2	Patients who do not respond to the following therapies (drug classes), are ineligible for them, or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline[b]	Valproic acid[c] or *Clostridium botulinum* toxin type A[d]	Added benefit not proven
3	Patients who do not respond to any of the following therapies (drug classes), are ineligible for them, or do not tolerate them: metoprolol, propranolol, flunarizine, topiramate, amitriptyline, valproic acid[c] or *Clostridium botulinum* toxin type A[d]	BSC[e]	Indication of considerable added benefit[f]

a: Presentation of the respective ACT specified by the G-BA.
b: All 4 drug classes defined as the ACT for research question 1 (beta blockers, flunarizine, topiramate, or amitriptyline) must have been considered before the patients fall under research question 2. Both valproic acid and *Clostridium botulinum* toxin type A are not standard options for all patients.
c: In accordance with the G-BA Drug Prescribing Directive, Section K, Annex VI: if treatment with all other drugs approved for the indication was unsuccessful or is contraindicated.
d: Only for chronic migraine in accordance with approval.
e: BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.
f: For deriving the added benefit, data are available from the LIBERTY study on patients with a mean of 9.1 migraine days/month. No patients meeting the ICHD-3 criteria for chronic migraine were included in the study.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; ICHD-3: International Classification of Headache Disorders, 3rd Edition

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-71-erenumab-prophylaxis-of-migraine-benefit-assessment-according-to-35a-social-code-book-v.10907.html.