

R E V I E W

The cost effectiveness of Erenumab in migraine therapy: A systematic review

Dhafer Alshayban

Pharmacy Practice Department, College of Pharmacy, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Abstract. *Background and aim:* Migraine is a common neurological condition that affects millions of people worldwide. Newly approved treatments for the prevention of migraine including calcitonin gene-related peptide monoclonal antibodies such Erenumab, might help in case of the failure of other medications. Therefore, it was decided to conduct a systematic literature review of cost effectiveness of Erenumab which is the first and most common medication among its group. *Methods:* Pharmacoeconomics studies which were written in English and published between 2015 and 2025 were included. Several databases such as Scopus, Web of Science, OVID Medline, Embase, PubMed, and Dimensions were searched independently. *Results:* Six published studies, and 2 reports were selected from an initial pool of 974 based on predefined inclusion criteria. They were conducted across different countries settings including the United States, United Kingdom, Sweden and Greece and, Spain. These studies adapted decision-analytic models, using either standalone Markov models or decision trees in combination with Markov models, adapted with country-specific data to evaluate the cost effectiveness of Erenumab. *Conclusions:* Erenumab's cost-effectiveness is context-dependent, varying according to local drug pricing, healthcare system structures, and patient populations. Evidence suggests that Erenumab is a cost-effective option for individuals with chronic or episodic migraine who have not responded to previous treatments. However, it was not cost effectiveness in countries such as Iran and Greece unless a significant discount in price was applied. Future research should prioritize pharmacoeconomics evaluations comparing Erenumab with newer agents, such as fremanezumab and galcanezumab, to support more informed policy and reimbursement decisions. (www.actabiomedica.it)

Key words: Cost effectiveness, Erenumab, Migraine, Pharmacoeconomics evaluation, Markov model

Introduction

Migraine is a common neurological condition that affects millions of people worldwide with approximate prevalence of migraines, which exceeds 1 billion cases. Migraine stands as the foremost cause of disability globally among individuals under the age of 50, with a particularly pronounced impact on women (1,2). Migraineurs usually suffer from recurring episodes of moderate-to-severe headache pain in one or two sides of the head which usually last from a few hours to days (1). These headache episodes can

interfere with daily life and work, potentially leading to a loss of productivity and making even simple tasks seem to be complicated (1,2). Patients with migraine usually report that the pain is more than just a headache as they consider it as a complex condition that can come with a range of other symptoms, such as nausea, sensitivity to light and sound, and sometimes even visual disturbances (1,2). The management of migraine incorporates both non-pharmacological and pharmacological interventions, offering a comprehensive approach to control this issue. Pharmacological treatment of migraine encompasses a both acute and preventive

treatment strategies. One way to treat acute migraine is to use modern treatment alternatives which include both small-molecule medications and biologic drugs that target and block calcitonin gene-related peptide (CGRP) signaling (3). Examples of these medications include Ubrogepant, and Zavegepant which are used for acute migraine therapy and Atogepant and Rimegepant that are used for preventive therapy (3). Furthermore, Erenumab is a monoclonal antibody that targets the Calcitonin gene-related peptide receptor antagonist (CGRPR), whereas Fremanezumab, Galcanezumab, and Eptinezumab are monoclonal antibodies that specifically bind to the CGRP peptide itself (3). These therapies are broadly used for the preventive treatment of migraine (3). Erenumab has a unique combination of clinical benefits compared to the available oral therapies, convenient use due to its long half-life that allows for longer dosing intervals, It is the first approved treatment among the CGRP receptor inhibitor medications for migraine prophylaxis and treatment. It has appeared as a promising preventive therapy for migraine that is used as subcutaneous injection at a dose of 70 mg (4,5,6). The efficacy and safety of Erenumab were clearly demonstrated in several placebo-controlled studies involving people with episodic migraine (EM) and chronic migraine in adults who have had ≥ 4 migraine days per month (4,5,6,7). In addition, it showed high effectiveness in the real-world studies (4,8). One advantage of Erenumab is its convenience with one monthly administration which has contributed to enhancing patients' adherence (6). However, it tends to be more expensive compared to other available medications which raise many questions about its cost-effectiveness (9). Given its high price, pharmacoeconomic evaluation of Erenumab is critical for informed decision making to determine whether the added value justifies the increased expense. While several studies have compared the cost-effectiveness of Erenumab with other types of migraine treatment, there are some gaps in the literature. First, most of the research is conducted in the high-income context, and data for low- and middle-income countries where cost is a key consideration is lacking. Second, there is an absence of consistency in methodological approaches, with variability in time horizons, perspectives, and cost inputs, that hinders

direct comparisons across studies. Hence, there is a necessity for conducting a systematic review to assess the cost-effectiveness of Erenumab. One systematic review examined the cost-effectiveness of migraine treatment but only in specific populations (UK and Ireland) (10). Another systematic review which was published in 2022 highlighted evidence supporting the cost-effectiveness of pharmacological interventions, specifically OnabotulinumtoxinA) and other migraine treatments including Erenumab, in the management of chronic migraine among the adult population (11). Nevertheless, since the previous systematic review was published in 2022, additional economic evaluations of Erenumab have emerged, including studies published as recently as 2024. To address this gap, the current review synthesizes the most recent available data, offering an updated assessment of Erenumab's cost-effectiveness in migraine management

Methods

A systematic search was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (12) and the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines (13,14).

Literature search and study selection

A detailed investigation was conducted on multiple electronic databases, Scopus, Web of Science, OVID Medline, Embase, PubMed, and Dimensions. Multiple databases were used to access diverse literature, cover different disciplines, reduce publication and selection bias, and confirm the effectiveness of the search strategy. We included publications from January 1, 2015, to February 1, 2025. For example, we searched PubMed using the following keywords: ("Migraine Disorders"[Mesh] OR migraine OR "Migraine prophylaxis" OR "Migraine Treatment") AND ("Cost-Benefit Analysis"[Mesh] OR "economic evaluation*" OR "cost effective*" OR "cost-utility*" OR "direct cost*" OR "indirect cost*" OR QALY OR icer OR economical OR affordable OR inexpensive OR "low-cost" OR reasonable OR cheap* OR "money-saving"

OR “Cost saving”) AND (erenumab OR aimovig OR Usual care OR topiramate OR Migraine prophylactic drugs, OR, surgical intervention) (economic* OR economic evaluation).

To ensure a comprehensive literature search, automatic snowballing searching was conducted on *citiful.xyz*, while manual search process was conducted on the google scholar and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) to find additional relevant studies. The reference lists of included studies were reviewed by the researchers to identify more pertinent studies.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were established based on the PICOS (Population, Intervention, Comparator, Outcomes, Study Design) framework. During the screening process, we focused on including articles written in English that examined the pharmacoeconomics concepts including both cost-effectiveness and cost-utility of Erenumab as compared with other medications used to treat migraine. Studies not meeting the following criteria were excluded: those not written in English, published before 2015, those unrelated to Erenumab; those involving participants under 18 years of age; and those pertaining to conditions other than migraine. Reviews, opinion pieces, systematic literature reviews (SLRs), scoping reviews, cohort studies, and case reports were not included.

Study selection

The literature search was carried out independently by two researchers, Dhafer Alshayban (DA) and Shakil Ahmed (SA). They carefully reviewed all the articles they found and cross-checked them to remove any duplicates. The review followed the PRISMA guidelines, which are widely recognized standards for conducting systematic reviews and meta-analyses. First, Rayyan’s application (15) was used for the title and abstract screening and removing duplications. Following the initial screening using the Rayyan application, the retrieved articles were independently assessed by a single reviewer to determine compliance with the inclusion criteria. Discrepancies were resolved through

discussion or, when necessary, adjudication by a third reviewer. Subsequently, full-text articles were evaluated for studies deemed potentially relevant based on title and abstract screening, or when abstracts lacked sufficient detail. Next, they moved on to reading the full text of studies that seemed relevant based on the initial screening or when the abstract did not provide enough information.

Population

We included all adult patients within the age range of 18 to 65 diagnosed with high-medium frequency episodic migraine or chronic migraine

Intervention

Erenumab (sold under the brand name Aimovig®, Erenumab-aooe) is a innovative treatment for adults who suffer from migraines. It’s a fully human monoclonal antibody that works by blocking the calcitonin gene-related peptide (CGRP) receptor, which plays a key role in migraine attacks. As the first of its kind to be approved, Erenumab offers a preventive option for migraine sufferers. It’s given as one dose (70 mg) every month as a simple subcutaneous injection and is designed for convenience.

Comparator

Placebo, Usual care, best supportive care (BSC) topiramate and OnabotulinumtoxinA

Outcomes

Outcomes measures include monthly migraine days (MMD), productivity loss, incremental cost-effectiveness ratios (ICER) (e.g. cost per quality-adjusted life year [cost QALY] gained).

Data extraction

A comprehensive data extraction method was conducted, using Excel tables, to extract all relevant information from the included studies. The extracted data included the basic information (e.g., authors and

year of publication), the characteristics of the participant (e.g., age and gender), intervention details (e.g., Migraine, Migraine prophylaxis, Migraine Treatment, Erenumab (aimovig), usual care, topiramate, OnabotulinumtoxinA, Migraine prophylactic drugs, Economic evaluation, Cost-effectiveness, cost-utility, QALY, ICER), outcome measures, and key findings related to Economic evaluations of pharmacological treatments for adults with chronic migraine. DA and SA conducted the data extraction, and any disagreements were resolved through discussion and/or third-party negotiation.

Quality of reporting assessment

To allow a comparison of economic assessment methods that applied in the included studies, the reporting quality of model-based economic assessments was examined by the Risk of Bias In Non-randomized

Studies of Interventions (ROBINS-I tool) which assess the risk of bias through different domains : bias due to confounding; bias in selection of participants; bias due to classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in selection of reported results (16). The quality assessment was performed by one reviewer (DM) first and then verified by a second reviewer (SA) for accuracy, consistency, and reliability in the assessment process.

Result

The process of study selection is shown in the PRISMA flow diagram (Figure 1). We firstly identified 974 studies through comprehensive database searching, including Scopus, Web of Science, Medline,

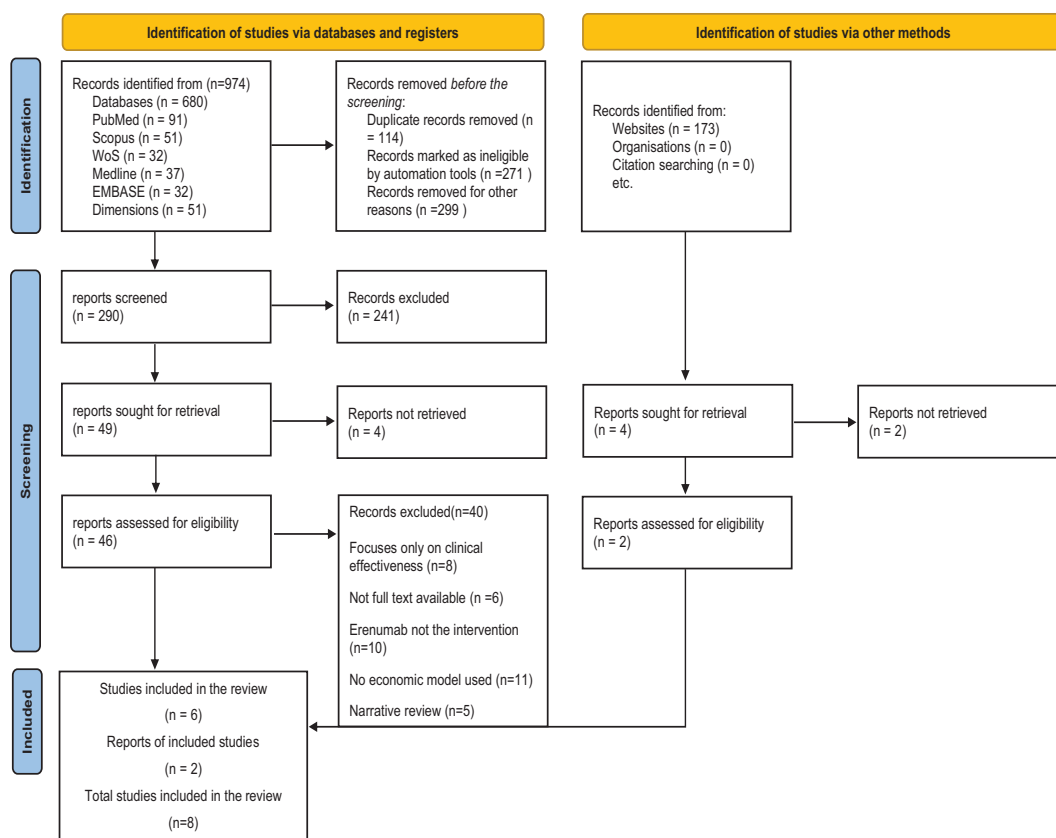


Figure 1. The PRISMA flow diagram

Embase, and Dimensions, along with additional sources of reference lists from eligible articles and. Following the removal of duplicate records, 290 distinct records were left for title and abstract screening. Through the screening process, 241 records were eliminated in accordance with pre-established exclusion criteria, such as irrelevance to the study question, publication in a non-English language, and non-peer-reviewed literature. Hence, 46 full-text articles remained for evaluation. Out of these, 40 articles were excluded based on inappropriate study design (e.g., Narrative reviews), absence of economic model, or focus only on clinical data and other reasons, 6 studies (17-22) fulfilled all the above inclusion criteria and 2 reports (11,23,24) were eligible for qualitative synthesis. The steps of the study selection, along with the reasons for the exclusion of full texts, are presented in the PRISMA flow diagram (Figure 1).

Health care setting, intervention and comparison arms, and types of cost-effectiveness evaluation

After applying the pre-defined inclusion and exclusion criteria, a total of 6 studies and two reports were found to be suitable for utilization in the systematic literature review. Two of the 6 studies retrieved through the database search were published in the most recent year (2024) (17,18). Interestingly, all the studies and reports included in this systematic review were conducted in USA and European countries (i.e., UK, Spain, Greece and Sweeden), however, one study was carried out in Iran by Mollae et al. (2024). The methods that used for all the studies included in this review were model-based studies. All these studies used one type of economic evaluation which was cost-utility analyses that involve hypothetical cohorts of the patients with chronic migraine. Among the included studies, one study (20) evaluated Erenumab directly with OnabotulinumtoxinA. Other studies (17-19,21,22) evaluated Erenumab compared the treatment with other alternatives including best supportive care, placebo, topiramate and OnabotulinumtoxinA. More information about the interventions and comparators is shown in Table 1. There were two other reports that used cost utility analysis to compare Erenumab with the best care, placebo and OnabotulinumtoxinA. One

of them was conducted in Canada (11,23) and another report (11,24) was conducted in UK.

The modeling technique, evaluation perspective, and time horizon incorporated in the models

Descriptions of economic modeling approaches and input variables are presented in Table 2. The included cost effectiveness analysis (CEA) was classified based on the following pharmacoeconomic aspects: type of economic evaluation, adapted perspective, time horizon, model used, cost and outcome unit, and sensitivity analysis. Cost utility analysis technique was the main type of Pharmacoeconomics evaluation used in all the included studies. A decision tree combined with a Markov model were deployed in the research articles (17,19,22) while Markov cohort model only was implemented in two studies (18,21) and only one study used only the decision-analytic tree model to estimate the potential outcomes of treating patients with chronic migraine (20). Patient cohorts were simulated using a three-state Markov model that included on-treatment, off-treatment, and death states to assess health outcomes (18,21,22). However, other studies used negative discontinuation as absorbing state instead of the death state (17,19). The model was conducted over a time horizon ranging from 2 to 10 years across the majority of the studies (17,19,20,21) with only two studies were limited to only 5 years (18,22). In terms of the perspective used, societal perspectives were employed in several studies (18, 19, 21) while other studies used both societal and payer points of view (20,22). Additionally, one study adopted a Spanish National Healthcare System perspective (17). The two reports included in this review used different models for evaluating the cost effectiveness of Erenumab (11,23,24). For instance, Canadian Agency for Drugs and Technologies in Health (CADTH) used a hybrid model structure, with a decision tree for the initial 12-week period to classify participants as responders or non-responders and a Markov model for the rest of the period, found on 12-week cycles (23). The report was conducted using the Canadian public healthcare payer perspective (11,23) while NICE report deployed a decision-tree plus Markov model where two health states were included: on treatment and discontinuation

Table 1. Summary of the characteristics of included studies.

Study ID	Study details: Author, year	Study design, Country	sample size	Study population	Intervention	Comparator	Type of economic evaluation
1	Pozo-Rosich et al., 2024 (17)	Cost-effectiveness analysis, Spain	1000	Patients with episodic and chronic migraine	Erenumab	Best supportive care (BSC) for episodic migraine, OnabotulinumtoxinA for chronic migraine	Cost-utility analysis
2	Mollace et al., 2024 (18)	Cost-utility analysis, Iran	1000	Patients with episodic and chronic migraine in Iran	Erenumab	Topiramate	Cost-utility analysis
3	Mahon et al., 2021 (19)	Cost-effectiveness analysis, Sweden	No specific patient sample	Patients with at least 4 monthly migraine days (MMDs) who had failed at least two prior preventive treatments	Erenumab	Best supportive care (BSC) (acute treatment only, e.g., triptans, analgesics), also included onabotulinumtoxinA as a comparator for chronic migraine (CM) patients	Cost-utility analysis
4	Giannouchos et al., 2019 (20)	Cost-effectiveness analysis, Greece	No specific patient sample	Patients with chronic migraine failed initial preventive treatment	Erenumab	OnabotulinumtoxinA	Cost-utility analysis
5	Lipton et al., 2018 (21)	Cost-effectiveness analysis, USA	No specific patient sample	Patients with episodic and chronic migraine who had failed at least one prior preventive therapy	Erenumab	Supportive care consisted of acute treatments only (e.g., triptans, analgesics, NSAIDs, and opioids), and Scenario Analysis with OnabotulinumtoxinA (Botox) for Chronic Migraine Patients	Cost-utility analysis
6	Sussman et al., 2018 (22)	Cost-effectiveness analysis, USA	Not stated	Patients with episodic migraine (EM) and chronic migraine (CM) undergoing preventive therapy	Erenumab	No preventive treatment (NPT) for episodic and chronic migraine; OnabotulinumtoxinA for chronic migraine	Cost-utility analysis
7	CADTH report 2019 (23)	Cost effectiveness Canada	Not specific	Pharmacoeconomic model	Erenumab	BSC OnabotulinumtoxinA	Cost-utility analysis
8	NICE report United Kingdom (UK) (24)	Cost effectiveness UK	439	Pharmacoeconomic model	Erenumab	BSC OnabotulinumtoxinA	Cost-utility analysis

Table 2. Descriptions of economic modeling approaches and input variables.

Study ID	Title of the study	Model used	Perspective	Time horizon	Cost included in the study	Currency, price year
1	Is erenumab an efficient alternative for the prevention of episodic and chronic migraine in Spain? (17)	Markov model	Healthcare system perspective	10 years	Direct and indirect costs	EUR, 2023
2	Cost-Utility Analysis of Erenumab Compared to Topiramate for Preventive Therapy of Migraine in Iran (18)	Markov model	Societal perspective	5 years	Direct and indirect costs	USD (\$), 2024
3	Cost-Effectiveness of Erenumab for the Preventive Treatment of Migraine in Patients with Prior Treatment Failures in Sweden (19)	Hybrid model (Decision-tree + Markov model)	Societal and healthcare system perspectives	10 years	Direct and indirect medical costs	SEK, 2019
4	Cost-Effectiveness Analysis of Erenumab Versus OnabotulinumtoxinA for Patients with Chronic Migraine Attacks in Greece (20)	Decision-tree model (validated using Markov modeling techniques from prior research)	Payer and societal perspectives	1 year	Direct costs: Drug acquisition costs, administration costs, acute treatment costs, hospitalization, physician visits, emergency department visits, Indirect costs (for societal perspective): Productivity loss due to absenteeism and presenteeism	Euro (€), 2019
5	Estimating the Clinical Effectiveness and Value-Based Price Range of Erenumab for the Prevention of Migraine in Patients with Prior Treatment Failures: A US Societal Perspective (21)	Markov model	US societal perspective	10 years	Direct and indirect costs and cost-effectiveness metrics	USD (\$), 2017
6	Cost-Effectiveness Analysis of Erenumab for the Preventive Treatment of Episodic and Chronic Migraine: Results from the US Societal and Payer Perspectives (22)	Hybrid model (Monte Carlo patient simulation + Markov cohort model)	Societal and payer perspectives	2 years	Direct and indirect costs and ICER analysis based on QALYs	USD, 2017
7	CADTH report 2019 (23)	Hybrid model with decision tree for 12-week assessment Period. Participants Were divided as responders and non-responders, and	Canadian public health care Payers perspectives	3 years	Cost that directly related to migraine. Hospitalizations, emergency department visits cost,	USD 2018
8	NICE report 2019 (24)	A decision-tree plus Markov model included. Responded and not responded patients were classified into two health states	NHS perspective	Lifetime	All Treatments that related to migraine cost. Hospitalization E-emergency room visit, and physicians visit cost and productivity losses (indirect cost)	UK pound 2018

of treatment (11,24). The report adopted the NHS viewpoint and evaluated costs and outcomes over a lifetime horizon.

The types of cost included and outcomes in the studies

The types of costs considered across all six studies were generally consistent which include direct and indirect cost. Examples of direct medical costs include treatment costs (3), hospitalizations, emergency room visits, appointments with specialists or primary care doctors, and concomitant medications cost (17,18,19,20,21). Direct non-medical cost such as the trip cost was also calculated in one study (18). Indirect costs, such as absenteeism and presenteeism (productivity loss) were included in all studies. Across all studies, the methodologies for data collection varied depending on the availability and relevance of the resources. In certain studies data pertaining to the use of resources were gathered from head-to-head studies, published literature, official data sources and placebo-controlled randomized trials. (17-19,21,22). One study derived the cost data from publicly available website for healthcare professionals in Greece (20). All included studies reported outcomes in terms of QALYs and the MMD. Pozo-Rosich and his colleagues calculated QALY using estimated utilities obtained from individual data collected from the trials (17). Another study estimated QALY based on changes in patients' health-related quality of life (HRQoL) (18). Two studies derived the QALY as estimated by EQ-5D scoring derived from the International Burden of Migraine Study (IBMS) (20,22). Another study used EQ-5D-3L measure to estimate the utilities and QALY (21).

Cost effectiveness evidence

Erenumab vs placebo, best care, and Topiramate

Table 3 presents a summary result of cost effectiveness parameters. In most of the Included studies where Erenumab was utilized as an intervention, it was linked to a favorable ICER and it was a cost-effective alternative for the prevention of episodic migraine (EM) and chronic migraine (CM) when compared

with placebo, supportive care and Topiramate for patients for whom previous preventive treatments failed (17,19,21,22). Erenumab showed its effectiveness by reducing the number of MMD. For example, in Spain patients who have EM, the mean MMD was initially estimated at 9.44 but it was reduced to 6.95 at 12 weeks, 7.23 at 24 weeks, and at 7.42 by 108 weeks after using Erenumab (1). In another study which was conducted in Greece, it was found that the mean MMD reduction at 12 weeks was greater for patients who used Erenumab as compared with those who used placebo and best supportive care (BSC) (20). The use of Erenumab was cost-effective compared to placebo, with an ICER €2,398 (1), €3,122.64/QALY gained (4) and €20,000 (6). For example, in the study by Pozo-Rosich et al., an increase in costs of €1813 and an increase in QALYs of 0.756 compared to placebo, resulted in an ICER of €2,398/QALY gained. Furthermore, utilization of Erenumab was cost effective when compared to utilization of Topiramate (17). Considering both cost and HRQoL, Erenumab displayed an increase in cost and QALY of € 4420 and at 0.2311 QALYs with respect to topiramate (17). However, in the study by Mollae et al 2024 concluded that Erenumab, compared to Topiramatenol was not cost effective in Iran (18). A study by Sussman et al, found that using Erenumab was linked with increases in QALYs gained of 0.10 per patient compared Non preventive treatment (NPT). From the societal perspective, utilizing Erenumab was associated with a cost savings of \$1949 / patient compared to NPT which made as dominant strategy compared to NPT. This means that Erenumab was cost-saving and more clinically effective compared to NPT (22). From payer perspectives, treatment with Erenumab led to increases in costs of \$2319 per patient compared to NPT yielding an ICER of \$23,079 per QALY gained (22).

Erenumab vs OnabotulinumtoxinA

A study by Giannouchos et al 2019 compared Erenumab versus OnabotulinumtoxinA found that the ICERs were €218,870 and €231,554 /QALY gained, and €620 and €656 per migraine episode avoided, from societal and payer perspectives, respectively (20). However, the price of Erenumab would need to be

Table 3. Summary results of cost effectiveness parameters.

Study	Intervention	Medications assessed	QALY	ICER cost/QALY Cost/MMD avoided	Threshold	Conclusion
1 Pozo-Rosich et al. 2024 (17)	Erenumab	placebo	0.756	€2,398/QALY gained €3/MMD avoided	Spanish threshold of €30,000/QALY	Erenumab was found to be a cost effective alternative for the prevention of EM and CM in Spain
		Topiramate	5.88	€26/MD avoided €19,122/QALY gained		
2 Mollae et al. 2024 (18)	Erenumab	Topiramate	3.64	\$78,923 QALY	\$2,456	The study concludes that preventive treatment of migraine with Erenumab, compared to Topiramate, is not costeffective in Iran based on current prices
3 Mahone et al. 2021 (19)	Erenumab	placebo	5.4853	SEK34,696 /QALY gained 43/MD avoided	€28,528 SEK300,000	erenumab is a cost-effective treatment for migraine with a willingness-to-pay threshold of SEK300,000 per QALY.
4 Giannouchos et al. 2019 (20)	Erenumab	onabotulinumtoxinA	0.017	€218,870/QALY from societal perspective €231,554 from Payers perspectives	equal to three times the local gross domestic product (GDP) per capita (€49,000),	Erenumab might be cost effective compared to OnabotulinumtoxinA from both the payer and the societal perspective, but only at a highly discounted price.
5 Lipton et al. 2018 (21)	Erenumab	supportive care	0.185	\$23,998.	\$100,000-\$200,000	Erenumab is predicted to reduce migraine-related direct and indirect costs, and increase QALYs compared to SC.
6 Sussman et al. 2018 (22)	Erenumab	Placebo NPT OnabotulinumtoxinA	0.04 0.01 0.4	\$122,167/QALY and 180,012 for EM from societal and payers' perspective respectively \$15,360/QALY and 65,720 for CM from societal and payers' perspective respectively	\$50,000, \$100,000, \$200,000 per QALY	The use of Erenumab may be a cost-effective approach to preventing monthly migraine days among patients with chronic migraine versus Onabotulinumtoxin A and no preventive treatment in the societal and payer perspectives, but is less likely to offer good value for money for those with episodic migraine

reduced to a maximum of €192 (from a societal perspective) or €173 (from a payer perspective) for the ICERs associated with Erenumab to fall below this threshold which was calculated as equivalent to three times the GDP per capita (€49,000) in Greece (20). Another study found that using Erenumab was linked with increases in QALYs gained of 0.03 per patient compared to OnabotulinumtoxinA (21). Considering the societal perspective, utilizing Erenumab was associated with incremental costs of \$478/ patient relative to OnabotulinumtoxinA, resulting in an ICER of \$15,360 per QALY gained (22). When considering the payer perspective, treatment with Erenumab was linked with incremental in costs of \$2046 per patient compared to OnabotulinumtoxinA, resulting in ICERs of \$65,720 per QALY gained. More information about the results of cost effectiveness parameters Erenumab are presented in table 3.

Sensitivity analysis

Different types of sensitivity analyses such as deterministic and probabilistic sensitivity analyses were conducted in all included modelling studies. They showed that these results were robust under variation in a range of assumptions. Different scenarios were performed such as the number of previous treatment failures, societal perspective, measurement of absenteeism/presentism. Tornado diagram was used in some studies with different parameters such as cost of Erenumab and other comparators, rate of using Erenumab 70 mg and 140mg, rate of cost and utility discount, MMD in Erenumab and other comparators.

Quality assessment

The details of the risk of bias assessments for each study and reports are presented in Fig 2. There was evidence of low risk of bias in six studies, moderate risk in two studies. Overall judgement indicating medium risk was mainly caused by the risk of bias in domains concerning selection of participants and bias in measurement of outcomes. Serious risk of bias was seen in the measurement of outcomes. Regarding confounding bias, we considered two studies with medium risk. Concerning bias due to selection of participants, we

considered two studies to have a moderate risk of bias. For only one study, there was no information on domains concerning bias in measurement of outcomes.

Discussion

Cost-effectiveness analysis, as a key method of pharmacoeconomics evaluation, has been extensively used by policy makers in different health care settings to evaluate competing interventions and ensure efficient resource allocation (25,26,27). Worldwide, several migraine treatments with diverse clinical efficacy and cost profiles are available, with Erenumab being the first-in-class therapy approved for improved migraine management and prevention (4, 28). This analysis focused on published pharmacoeconomic analyses of the cost-effectiveness of the use of Erenumab medications for chronic and episodic migraine. A total of 974 studies were extracted. Based on our inclusion and exclusion criteria, six studies and 2 reports were included. The 6 studies were published between 2015 and 2024 in different countries including USA, UK, Greece, Spain, Sweden, and Iran. To the best of our knowledge, only two recent systematic reviews have assessed the cost-effectiveness of migraine medications. The first focused on studies conducted in the UK and Ireland [10], while the second provided a broader evaluation, involving all available migraine treatments without focusing on a specific medication (11). In contrast, the current systematic review is considered the first review that offers targeted evidence on the cost effectiveness of Erenumab in treating and preventing chronic and episodic migraine. In this review, the evidence on the cost-effectiveness of Erenumab for treating was systematically reviewed and assessed. Economic evaluation evidence suggests that Erenumab is a cost-effective option for the prevention and treatment of both chronic and episodic migraine, particularly among patients who have not responded to prior preventive medications. In fact, treatment with Erenumab was associated with a reduction in MMD and improvement in the QALY compared to the previous therapies. This result is aligned with other studies that documented that using calcitonin gene-related peptide monoclonal antibodies such as Erenumab is a better

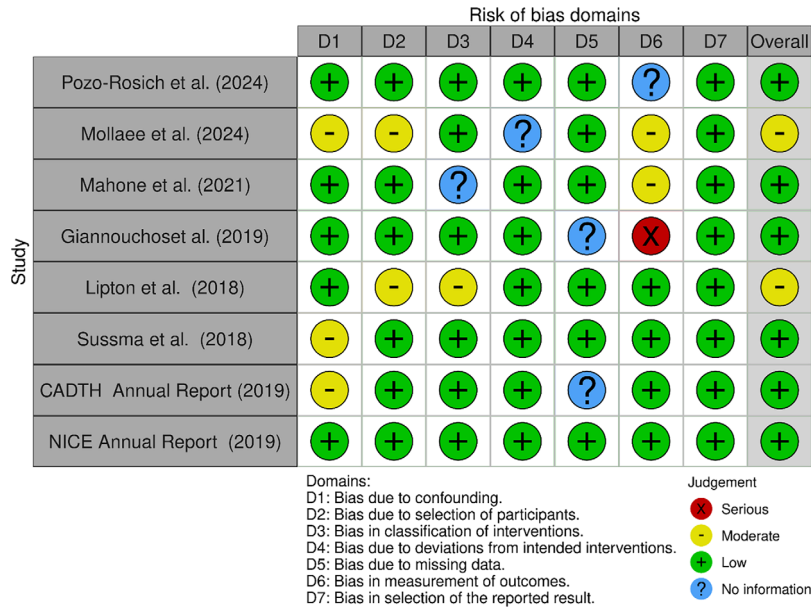


Figure 2. ROBINS-I risk of bias assessment.

choice for those who have previously failed two or more prophylactic treatments (29,30). Sussman et al, conducted a hybrid Monte Carlo patient simulation and Markov cohort model to assess the cost-effectiveness of Erenumab. Their results suggested that with an annual drug price of US\$6,900, Erenumab was cost-effective for reducing CM and enhancing the QALY for patients with chronic migraine compared with no treatment and OnabotulinumtoxinA (22). However, it may not represent a cost-effective option for individuals with episodic migraine (22). Erenumab may offer only modest clinical benefits and economic savings compared to alternative treatments. Several evidence suggested that Erenumab may not be a cost-effective option for the treatment of episodic migraine when compared with Topiramate (18). A study by Mollaei et al indicated that the ICER was calculated at \$78,923 QALY, which, when was above the Iranian WTP threshold of \$2,456. This result suggested that Erenumab is not cost effective when it is compared to Topiramate (18). One study assessed the cost effectiveness of Topiramate which is the most anti-epileptic drug that is frequently used in the management of migraine against different anti-epileptic medications such as Gabapentin, and Divalproex sodium (31). In a comparative analysis between Erenumab and

OnabotulinumtoxinA, one study suggested that the annual difference in costs between the two Erenumab and OnabotulinumtoxinA was €3720, and ICER was calculated at €218,870 per QALY gained which exceed the Greece WTP threshold (20). It is important to note that the studies that suggesting Erenumab was no cost effectiveness were conducted with settings characterized by low WTP while most of the other evaluations where Erenumab was considered cost effective were conducted in settings with higher WTP. A study by Gaviria and Hamid suggested that OnabotulinumtoxinA may be particularly beneficial for patients who are not eligible for CGRP mAb therapy or those who require localized treatment with minimal risk of systemic exposure (32). All the pharmacoeconomics evaluations in this systematic review were based on models. These studies were classified based on different criteria including type of economic evaluation, perspective, time horizon, model used, the cost and outcome unit, and the sensitivity analysis. Most of the models used combination of decision tree and Markov models which has three health states (e.g. on-treatment, off-treatment, and death) (18,21,22). Most of the studies used a societal perspective which is recommended for economic evaluation studies (33). The societal perspective is deemed as the gold standard in

pharmacoeconomic studies because it captures a more comprehensive range of costs and outcomes, including those that extend beyond the healthcare system (33). Studies included in this review employed additional costs such as the indirect cost. The significant impact of indirect costs on the results is estimated and important to consider because productivity-related losses (presenteeism) and absenteeism contribute to 60–70% and it might reach up to 90% of the overall economic burden of migraine (17,19,20). However, the exclusion of indirect costs did not render Erenumab cost-ineffective; in fact, it remained cost-effective for patients with chronic migraine when compared with no treatment (ICER US\$23,079/QALY) and OnabotulinumtoxinA (US\$65,720/QALY). The main strength of this review is the comprehensiveness of the study selection process and inclusion and exclusion criteria following PRISMA guidelines and using quality assessment tools (ROBINS-I) for each study included in this review which contributed to a strong review of the included studies. Another strength of this review is that it might offer clear targeted evidence into the cost-effectiveness of Erenumab which might help decision makers for better choice of the right intervention for managing migraine. Furthermore, we have included different studies across low-, medium- and high-income countries, with a diversity of perspectives (e.g. social, third party, government), and time horizon ranging from 2 years to lifetime. Our systematic review has several limitations. First, several assumptions that were made in structuring the Markov models which could have had an impact on the findings. For example, it was assumed that the patients in the treatment state remained in that state until discontinuation due to side effects. Conversely, participants in the off-treatment state were presumed not to receive any preventive treatment and used only palliative therapy for migraine at the same frequency as on treatment patients experiencing migraine. These assumptions may be internally inconsistent and could have influenced the validity of the model's final results. Another limitation of our review is that a hypothetical cohort of patients with EM and patients with CM with previous more than two medications failed were considered in some of the included studies. Although most decision

analytic modeling for cost effectiveness analyses usually use hypothetical cohort, interpretation of results should be done with caution, as findings may vary when applied to real-world populations. In addition, this study is constrained by its reliance on data from published studies alone, which may lead to the ignoring of important unpublished information. The last limitation of this review is generalizability. While different studies from different countries were included in this review, the results may not be generalized to other countries due to variations in medications availability, reimbursement policies and pricing of medications.

Conclusion

This systematic review provides more comprehensive and targeted insights into the cost effectiveness of Erenumab in managing and preventing CM and EM. Based on the results of this systematic review, Erenumab shows different levels of cost-effectiveness for migraine prevention across different countries and patient populations. It was cost-effective for the prevention of CM and EM, mainly in individuals who have failed previous preventive medications such as placebo, best supportive care (BSC), and onabotulinumtoxinA in countries like USA, UK, Spain and Sweden. In Greece, it could be considered as a cost-effective compared to onabotulinumtoxinA for CM, but only at a significant reduction in price. Nevertheless, Erenumab was not cost-effective compared to Topiramate in Iran unless a huge discount in price was made. Future research should focus on comparing Erenumab's cost-effectiveness against newer medications such as fremanezumab, galcanezumab to provide more informed decisions for policy makers.

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Correspondence:

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Dhafer Mahdi Alshayban, Msc, PhD

College of Pharmacy, Imam Abdulrahman Bin Faisal University, King Faisal Road, 34212, Dammam, Saudi Arabia

E-mail: dmalshayban@iau.edu.sa

ORCID: 0000-0001-8389-7287