Fremanezumab
The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.
Rejected
Section:
5. Medicines for neurological disorders 5.1. Medicines for central nervous system disorders 5.1.5. Medicines for headache disorders 5.1.5.2. Medicines for migraine prophylaxis
ATC codes: N02CD03
Indication
Chronic migraine ICD11 code: 8A80.2
INN
Fremanezumab
Medicine type
Chemical agent
List type
Core
Formulations
Parenteral > General injections > SC: 225 mg per 1.5 mL in pre-filled syringe
EML status history
Application rejected in 2025 (TRS 1064)
Sex
All
Age
Adolescents and adults
Therapeutic alternatives
erenumab (ATC codes: N02CD01)
eptinezumab (ATC codes: N02CD05)
galcanezumab (ATC codes: N02CD02)
Patent information
Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org
Read more about patents.
Tags
Biological
Wikipedia
Fremanezumab
DrugBank
Fremanezumab
Expert Committee recommendation
☐
The Expert Committee noted that migraine is a common primary headache disorder characterized by recurrent moderate to severe pain and acknowledged the public health relevance of effective treatments. Migraine is a cause of considerable disability and results in a substantial socioeconomic burden, which is greater for women than for men. Migraine prophylaxis is generally recommended in the presence of at least four migraine days per month and/or when migraine substantially affects quality of life. The Committee acknowledged the importance of preventive treatment in people with chronic migraine, occurring in about 2% of the population and defined as at least 15 days with headache per month for at least 3 months. With daily or near-daily attacks, people with chronic migraine have functional impairment and a lower quality of life. The Committee noted that multiple randomized, double-blind, placebo-controlled trials demonstrated the benefits of fremanezumab over placebo in reducing the monthly average migraine days and increasing the ≥ 50% responder rate in patients with episodic and chronic migraine. Subgroup analyses (e.g. based on previous treatment failures) also suggested that fremanezumab was effective in refractory populations and may improve disability and quality of life. The Committee considered that the magnitude of benefit of fremanezumab over placebo was moderate and greater in patients with episodic migraine than chronic migraine. Adverse events of fremanezumab were generally mild to moderate in severity and were manageable. The Committee also noted the findings of a recent systematic review and network meta-analysis of the different classes of medicine for migraine prophylaxis which reported high-, moderate-, and low-certainty evidence (depending on the comparator) that fremanezumab may have a greater effect and a better safety profile than medicines from other classes. However, the review did not include trials involving fremanezumab in direct head-to-head comparisons with other medicines (e.g. propranolol); therefore, the Committee was unable to determine the magnitude of benefit of fremanezumab versus the currently listed prophylactic treatment. The Committee noted that fremanezumab was considerably more expensive than propranolol and concluded that, in the absence of clear evidence demonstrating a proportional improvement in outcomes, the cost difference could not be justified to support a recommendation to list on the EML at this time. The Committee also noted the current limited global availability of the medicine and that biosimilar versions are not yet available. Based on these considerations, the Expert Committee did not recommend the inclusion of fremanezumab on the EML for prophylaxis of high-frequency or chronic migraine.
Background
☐
The application proposed the addition of fremanezumab with a square box as representative of the pharmacological class of anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies to the core list of the EML for preventive treatment of high-frequency and chronic migraine in adults. Proposed therapeutic alternatives were erenumab, eptinezumab and galcanezumab. Neither fremanezumab nor other anti-CGRP monoclonal antibodies have previously been evaluated for inclusion on the Model Lists. The EML currently includes only propranolol (with a square box) for migraine prophylaxis.
Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise and odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (1). In about 25% of people affected, episodes may be preceded by transient focal neurological symptoms (most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits). The global prevalence of migraine is estimated at 14–15% (more than 1 billion people worldwide) and it is two to three times higher in women than men (2). According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (3). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (4). Chronic migraine is defined as 15 or more headache days per month for at least 3 months (5). About 3% of the general population experiences chronic migraines and each year, 2–3% of people with episodic migraine (fewer than 15 headache days per month) transition to a chronic migraine state (6, 7).

Benefits

The application presented the results of a systematic literature review and meta-analysis conducted for the purpose of the application. For the analysis of efficacy, the outcome measures were: change in monthly headache/migraine days (defined as the variation in days reported by participants from baseline to the end of follow-up as reported in headache diaries); and ≥ 50% responder rate (defined as the proportion of participants reporting a ≥ 50% reduction in monthly headache/migraine days compared with baseline). The ≥ 50% reduction of monthly attacks was also considered for ≥ 50% responder rate when the reduction in monthly headache/migraine days was not available. Overall, 27 studies were included in the quantitative synthesis, of which eight assessed fremanezumab. Episodic migraine Four randomized controlled trials compared fremanezumab to placebo in patients with episodic migraine (8–11). For the outcome of change in monthly migraine days at 12 weeks, the pooled analysis showed benefits of fremanezumab 225 mg monthly (standardized mean difference (SMD) −0.56, 95% confidence interval (CI) −0.76 to −0.36) and fremanezumab 675 mg quarterly (SMD −0.56, 95% CI −0.86 to −0.26) over placebo. For the outcome of ≥ 50% responder rate, both dosages of fremanezumab were associated with benefit compared with placebo (225 mg: risk ratio (RR) 2.02, 95% CI 1.38 to 2.97; 675 mg: RR 2.07, 95% CI 1.32 to 3.26). In absolute terms, 256 more per 1000 (95% CI 95 more to 493 more) for 225 mg and 336 more per 1000 (95% CI 7 fewer to 1000 more) for 675 mg. The quality of evidence for both outcomes was high. Chronic migraine Four randomized controlled trials compared fremanezumab to placebo in patients with chronic migraine (10, 12–14). Fremanezumab 225 mg monthly was associated with benefits over placebo for change in monthly migraine days (SMD −0.39, 95% CI −0.62 to −0.16) and ≥ 50% responder rate (RR 2.11, 95% CI 1.70 to 2.63). In absolute terms this means 199 more responders per 1000 (95% CI 135 more to 279 more). The quality of evidence for both outcomes was moderate, downgraded due to the use of a 675 mg loading dose that is not approved for clinical use. Fremanezumab 675 mg quarterly was associated with benefits over placebo for change in monthly migraine days (SMD −0.34, 95% CI −0.58 to −0.09), and ≥ 50% responder rate (RR 2.08, 95% CI 1.73 to 2.51). In absolute terms, 182 more per 1000 (95% CI 115 more to 267 more). The quality of evidence for both outcomes was high. No evidence was presented in the application addressing the benefits of other anti-CGRP monoclonal antibodies.

Harms

According to the European Medicines Agency’s summary of product characteristics for fremanezumab, more than 2500 patients have been treated with fremanezumab in registration studies, representing more than 1900 patient-years of exposure. More than 1400 patients were treated for at least 12 months. The most commonly reported adverse drug reactions were local injection-site reactions: pain (24%), induration (17%), erythema (16%) and pruritus (2%). These events were reported to be transient, predominantly mild to moderate in severity and generally did not necessitate treatment discontinuation. Anaphylactic hypersensitivity reactions were reported rarely. In placebo-controlled studies, 6/1701 (0.4%) patients treated with fremanezumab developed anti-drug antibodies, one of whom who developed neutralizing antibodies. Antibody responses were of low titre. With 12 months of treatment, anti-drug antibodies were detected in 43/1888 (2.3%) patients with 0.95% of the patients developing neutralizing antibodies. The safety and efficacy of fremanezumab were not affected by development of anti-drug antibodies (15). A 2023 systematic review of 19 randomized controlled trials (14 584 participants) compared the safety and tolerability of monoclonal antibodies targeting the calcitonin gene-related peptide pathway and small molecule gepants in migraine prevention (16). From the network meta-analysis, significantly greater odds of treatment-emergent adverse events were associated with fremanezumab 225 mg (odds ratio (OR) 1.21, 95% CI 1.02 to 1.42), fremanezumab 675 mg (OR 1.20, 95% CI 1.02 to 1.41), galcanezumab 120 mg (OR 1.40, 95% CI 1.16 to 1.70) and galcanezumab 240 mg (OR 1.63, 95% CI 1.33 to 2.00). No significant differences were found between anti-CGRP monoclonal antibodies and placebo for serious adverse events. Eptinezumab was associated with the lowest odds of treatment-emergent adverse events and serious adverse events compared with placebo. Erenumab was associated with the lowest odds of any adverse events. Both doses of erenumab and fremanezumab had the lowest odds of adverse events leading to treatment discontinuation. A 2023 retrospective analysis evaluated adverse events associated with erenumab, fremanezumab and galcanezumab spontaneously reported to the adverse event reporting system of the United State Food and Drug Administration in the first 6 months of launching the medicines (17). The most commonly reported adverse events per 1000 exposed patients for erenumab were wrong technique, constipation and migraine. The most commonly reported adverse events per 1000 exposed patients for fremanezumab were headache, drug ineffectiveness and migraine. The most commonly reported adverse events per 1000 exposed patients for galcanezumab were injection-site pain, underdose and headache.

Additional evidence

A 2023 systematic review and network meta-analysis (74 randomized controlled trials, 32 990 participants) assessing the comparative effectiveness of different migraine preventive medicines was identified during the application review process (18). Medicine classes Included were antidepressants, antiepileptics, antihypertensives, anti-CGRP monoclonal antibodies, calcium channel blockers and gepants. Anti-CGRP monoclonal antibodies were found to be the most effective class for increasing the proportion of patients achieving a ≥ 50% reduction in monthly migraine days and reducing the number of monthly migraine days. Fremanezumab was the most effective within in its class for these outcomes. For adverse events leading to discontinuation, anti-CGRP monoclonal antibodies were not different compared with placebo.

Cost / cost effectiveness

☐

The application reported current wholesale prices provided by Teva Pharmaceuticals for fremanezumab 225 mg injection as 102.05 euros (€) in Argentina and €786.27 in the United States of America. A 2022 systematic review evaluated economic evaluations of pharmacological treatments for adults with chronic migraine (19). Sixteen model-based cost-utility studies were included which evaluated botulinum toxin (n = 6), erenumab (n = 8), fremanezumab (n = 2) and galcanezumab (n = 1) as the main treatment. Of the two studies evaluating fremanezumab, a United States study reported the incremental cost–effectiveness ratio for fremanezumab versus no preventative treatment to be 115 000 United States dollars (US$) per quality-adjusted life year (QALY), well above the baseline willingness-to-pay threshold of US$ 50 000/QALY. A evaluation by the United Kingdom's National Institute for Health and Care Excellence (NICE) reported incremental cost–effectiveness ratios for fremanezumab of 11 825 pounds sterling (£)/QALY versus best supportive care and £16 227/QALY versus botulinum toxin type A. The NICE technology appraisal concluded that the most plausible incremental cost–effectiveness ratio for fremanezumab compared with best supportive care for episodic migraine after failure of three preventive treatments was below £20 000 per QALY gained. Fremanezumab was considered to be a cost-effective use of National Health Service resources for people with episodic migraine in whom three preventative treatments had failed. With regard to chronic migraine, uncertainties remained about the clinical effectiveness of fremanezumab; however, fremanezumab was considered likely to be a cost-effective use of National Health Service resources for preventing chronic migraine after three preventive treatments had failed. Subsidized supply of fremanezumab in the United Kingdom is subject to a commercial arrangement with the manufacturer (20). A 2024 company-sponsored analysis in the Kingdom of the Netherlands evaluated the cost–effectiveness of fremanezumab versus best supportive care in patients with chronic migraine and inadequate response to previous preventive therapy from a societal perspective including direct and indirect costs (21). The base-case analysis, which compared fremanezumab with best supportive care (acute migraine treatment only) in patients with chronic migraine and an inadequate response to topiramate or valproate and onabotulinumtoxinA over a lifetime horizon, relied on data from a post hoc subgroup analysis of 138 patients from the FOCUS trial (22). The results from the base-case analysis found fremanezumab to be dominant strategy. A supportive analysis using data from the full FOCUS population with chronic migraine (509 patients) (10) found fremanezumab was cost-effective compared with best supportive care with an incremental cost–effectiveness ratio of €2547/QALY gained. Fremanezumab remained cost-effective in all sensitivity and scenario analyses. A 2024 company-sponsored analysis evaluated the cost–effectiveness of fremanezumab compared with standard care in previously treated patients with episodic and chronic migraine over a 25-year horizon from a Japanese health-care perspective (23). Incremental cost–effectiveness ratios for fremanezumab versus standard care were 6 334 861 Japanese yen (¥) (~US$ 41 345) for episodic migraine, ¥7 393 824 (~US$ 48 257) for chronic migraine and ¥6 530 398 (~US$ 42 621) for the total migraine population (weighted average of 70% episodic and 30% chronic). Higher incremental cost–effectiveness ratios of ¥9 442 917 to ¥9 952 007 (~US$ 61 630 to US$ 64 953) were found in scenarios that excluded productivity losses. Assuming a willingness-to-pay threshold of ¥5 million (~US$ 32 633), fremanezumab would have about a 26% chance of being cost effective compared with standard care.

WHO guidelines

☐

WHO guidelines for the prevention of high frequency and chronic migraine are not currently available. The application provided a brief summary of recommendations related to anti-CGRP monoclonal antibodies as preventive treatment for episodic or chronic migraine from various current national and international clinical guidelines.

Availability

☐

A survey conducted among members of the International Headache Society reported that fremanezumab was available in 29 upper-middle and high-income countries globally. Biosimilar versions are not currently available.

Other considerations

☐

The Department of Mental Health, Brain Health and Substance Use provided comments on the application. The technical department noted that evidence from direct head-to-head comparisons with currently used oral migraine prophylaxis treatments was not presented in the application and highlighted the high cost of anti-CGRP monoclonal antibodies.

☐ Show references Hide references

1. Steiner TJ, Stovner LJ. Global epidemiology of migraine and its implications for public health and health policy. Nat Rev Neurol. 2023;19(2):109–17 (https://doi.org/10.1038/s41582-022-00763-1). 2. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain. 2022;23(1):34 (https://doi.org/10.1186/s10194-022-01402-2). 3. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol. 2024;23(4):344–81 (https://doi.org/10.1016/s1474-4422(24)00038-3). 4. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):954–76 (https://doi.org/10.1016/s1474-4422(18)30322-3). 5. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211 (https://doi.org/10.1177/0333102417738202). 6. Katsarava Z, Schneeweiss S, Kurth T, Kroener U, Fritsche G, Eikermann A et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology. 2004;62(5):788–90 (https://doi.org/10.1212/01.wnl.0000113747.18760.d2). 7. Buse DC, Greisman JD, Baigi K, Lipton RB. migraine progression: a systematic review. Headache. 2019;59(3):306–38 (https://doi.org/10.1111/head.13459). 8. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015;14(11):1081–90 (https://doi.org/10.1016/S1474-4422(15)00249-5). 9. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA. 2018;319(19):1999–2008 (https://doi.org/10.1001/jama.2018.4853). 10. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet.

2019;394(10203):1030–40 (https://doi.org/10.1016/S0140-6736(19)31946-4). 11. Sakai F, Suzuki N, Kim BK, Tatsuoka Y, Imai N, Ning X et al. Efficacy and safety of fremanezumab for episodic migraine prevention: multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. Headache. 2021;61(7):1102–11 (https://doi.org/10.1111/head.14178). 12. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015;14(11):1091–100 (https://doi.org/10.1016/S1474-4422(15)00245-8). 13. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med. 2017;377(22):2113–22 (https://doi.org/10.1056/NEJMoa1709038). 14. Sakai F, Suzuki N, Kim BK, Igarashi H, Hirata K, Takeshima T et al. Efficacy and safety of fremanezumab for chronic migraine prevention: multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. Headache. 2021;61(7):1092–101 (https://doi.org/10.1111/head.14169). 15. Summary of product characteristics. AJOVY, INN-fremanezumab. Amsterdam: European Medicines Agency; 2023 (https://www.ema.europa.eu/en/documents/product-information/ajovy-epar-product-information_en.pdf). 16. Messina R, Huessler EM, Puledda F, Haghdoost F, Lebedeva ER, Diener HC. Safety and tolerability of monoclonal antibodies targeting the CGRP pathway and gepants in migraine prevention: Aasystematic review and network meta-analysis. Cephalalgia. 2023;43(3):3331024231152169 (https://doi.org/10.1177/03331024231152169). 17. Silberstein SD, Reshef S, Cohen JM, Gandhi S, Seminerio M, Ramirez Campos V et al. Adverse events reported with therapies targeting the cgrp pathway during the first 6 months post-launch: a retrospective analysis using the FDA Adverse Events Reporting System. Adv Ther. 2023;40(2):445–59 (https://doi.org/10.1007/s12325-022-02346-4). 18. Lampl C, MaassenVanDenBrink A, Deligianni CI, Gil-Gouveia R, Jassal T, Sanchez-Del-Rio M et al. The comparative effectiveness of migraine preventive drugs: a systematic review and network meta-analysis. J Headache Pain. 2023;24(1):56 (https://doi.org/10.1186/s10194-023-01594-1) 19. Khanal S, Underwood M, Naghdi S, Brown A, Duncan C, Matharu M et al. A systematic review of economic evaluations of pharmacological treatments for adults with chronic migraine. J Headache Pain. 2022;23(1):122 (https://doi.org/10.1186/s10194-022-01492-y). 20. Fremanezumab for preventing migraine. London: National Institute for Health and Care Excellence; 2022 (Technology appraisal guidance TA764; https://www.nice.org.uk/guidance/ta764). 21. Wolters S, Carpay JA, Pronk MH, Zuurbier KWM, Driessen MT, Lyras L et al. A Dutch cost-effectiveness analysis of fremanezumab versus best supportive care in patients with chronic migraine and inadequate response to prior preventive therapy. BMC Neurol. 2024;24(1):214 (https://doi.org/10.1186/s12883-024-03697-x). 22. Ferrari MD, Zuurbier KWM, Barash S, Ning X, Cohen JM. Fremanezumab in individuals with chronic migraine who had inadequate response to onabotulinumtoxinA and topiramate or valproic acid. Headache. 2022;62(4):530–3 (https://doi.org/10.1111/head.14294). 23. Takeshima T, Sakai F, Wang X, Yamato K, Kojima Y, Zhang Y et al. Cost effectiveness of fremanezumab in episodic and chronic migraine patients from a Japanese healthcare perspective. Pharmacoeconomics. 2024;42(7):811–22 (https://doi.org/10.1007/s40273-024-01380-0).