Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2226

fremanezumab 225mg solution for injection in pre-filled syringe (Ajovy®)

Teva UK Limited

6 December 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

fremanezumab (Ajovy®) is accepted for restricted use within NHSScotland.

Indication under review: For prophylaxis of migraine in adults who have at least four migraine days per month.

SMC restriction: for the treatment of patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments.

Three phase III studies demonstrated superiority of fremanezumab over placebo in reducing the number of monthly migraine days in patients with chronic and episodic migraine.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

For prophylaxis of migraine in adults who have at least four migraine days per month.[1]

Dosing Information

Treatment is intended for patients with at least four migraine days per month when initiating treatment with fremanezumab. Two dosing options are available:

- 225mg once monthly (monthly dosing) or
- 675mg every three months (quarterly dosing)

Fremanezumab is for subcutaneous injection only. Patients may self-inject if instructed in subcutaneous self-injection technique by a healthcare professional.
When initiating treatment with fremanezumab, concomitant migraine preventive treatment may be continued if considered necessary by the prescriber. When switching dosing regimens, the first dose of the new regimen should be administered on the next scheduled dosing date of the prior regimen.
The treatment benefit should be assessed within three months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter.
Treatment should be initiated by a physician experienced in the diagnosis and treatment of migraine.

Refer to the Summary of product characteristics (SPC) for further details.[1]

Product availability date

July 2019

Summary of evidence on comparative efficacy

Fremanezumab is a humanised monoclonal antibody which selectively binds the neuropeptide calcitonin gene-related peptide (CGRP) ligand and blocks both CGRP isoforms from binding to the CGRP receptor. CGRP is associated with vasodilation, inflammation and modulation of the transmission of pain. Levels of CGRP increase significantly during migraine and return to baseline levels with headache relief. The mechanism of action by which fremanezumab has its effect on migraine prevention is uncertain; it may be through modulation of the trigeminal system.[1, 2] The submitting company has requested that SMC considers fremanezumab when positioned for use in patients with chronic and episodic migraine who have had three or more prior migraine preventive treatment failures.

The key evidence to support the efficacy and safety of fremanezumab comes from a randomised, double-blind, placebo-controlled, phase IIIb study (FOCUS) in patients with episodic and chronic migraine who had an inadequate response to two to four previous classes of preventive therapy.[3]

The study included patients aged 18 to 70 years with episodic or chronic migraine who had documented failure to two to four classes of migraine preventive medications in the past 10 years. Treatment failure was defined as: no clinically meaningful improvement after at least three months of therapy at a stable dose, discontinuation due to intolerable adverse events, treatment contraindication, or unsuitable for the preventive treatment of migraine in the opinion of the treating clinician.[3, 4] Patients were required to have a history of migraine for at least 12 months before screening. Episodic migraine was defined as headache on ≥6 days but <15 days per month, with ≥4 days fulfilling any of the following criteria: migraine with aura or without aura, probable migraine, or use of triptans or ergot derivatives to treat an established headache. Chronic migraine was defined as headache on ≥15 days per month, with ≥8 days fulfilling the migraine criteria as listed for episodic above. Patients with and without overuse of acute headache medicines were also included.[3]

Patients were randomised equally to fremanezumab 675mg subcutaneously administered once every three months (n=276), fremanezumab 225mg subcutaneously monthly (except patients with chronic migraine who received 675mg in month 1 only, n=283), or placebo (n=279) for 12 weeks. Patients in all treatment groups received matching placebo injections to maintain blinding.[3] Randomisation was stratified by migraine classification (chronic or episodic), sex, country, number of previous preventive medicine classes (2, 3 or 4) and difficult to treat migraine (measured by proxy, if patients had previously received valproic acid or valproate or not).[3]

The primary outcome was mean change from baseline in the monthly average number of migraine days during the 12-week treatment period. A migraine day was defined as a calendar day with ≥4 consecutive hours of a migraine with or without aura as per ICHD-3 diagnostic criteria[5] or a headache, regardless of duration, treated with an acute migraine-specific medicines such as triptans or ergot compounds. The primary analysis was conducted in the modified intention-to-treat population. A hierarchical testing procedure was applied to control for multiplicity for the primary and secondary outcome analyses.

Quarterly and monthly fremanezumab regimens were associated with significantly greater reductions from baseline in monthly average migraine days, over 12 weeks, compared with placebo. These results were for the overall study population, including patients with chronic and episodic migraine and are described in greater detail in Table 1.[3]

Table 1. Results for the primary outcome and key secondary outcome of the FOCUS study (modified ITT population).[3]

	Fremanezumab monthly (n=283)	Fremanezumab quarterly (n=276)	Placebo (n=279)
Primary outcome			
Mean monthly number of migraine days at baseline	14.1	14.1	14.3
Reductions in mean monthly migraine days over 12 weeks, LSM, (SE)	−4·1 (0·34)	−3·7 (0·3)	−0·6 (0·3)
Difference in LSM versus placebo, (95% CI)	−3·5 (−4·2 to −2·8)[A]	−3·1 (−3·8 to −2·4)[A]	
Secondary outcome			
Proportions of patients with ≥50% reduction in mean monthly migraine days	34%[A]	34%[A]	9%

[A]comparisons of fremanezumab with placebo produced statistically significant differences, all p-values were <0.001, favouring fremanezumab. CI=confidence interval, LSM=Least squares mean, modified ITT population= all randomised patients who received at least one dose of study medicine and had at least 10 days of post-baseline efficacy assessments for the primary outcome, SE=standard error.

The results of the key secondary outcomes were consistent with the primary outcome. Statistically significant differences indicating a benefit of treatment with fremanezumab over placebo were reported for mean change from baseline in monthly average number of headache days of at least moderate severity (fremanezumab monthly, fremanezumab quarterly and placebo resulted in reductions of -4.2, -3.9 and -0.6 respectively), and mean change from baseline in monthly average number of days of use of any acute headache medications (fremanezumab monthly, fremanezumab quarterly and placebo resulted in reduction of -3.9, -3.7 and -0.6 respectively).[3]

To support the proposed positioning, the company presented descriptive results from post-hoc subgroup analyses of patients with episodic and chronic migraine who have failed three or more classes of preventive therapy.

Analyses of patient-reported outcomes were pre-specified exploratory analyses. The outcomes reported included 6-item Headache Impact Test (HIT-6); Migraine Disability Assessment (MIDAS); Migraine-Specific Quality of Life (MSQOL); EuroQol-5 Dimension (EQ-5D) 9-item Patient Health Questionnaire (PHQ-9); Work Productivity and Activity Impairment (WPAI); and patient Global Impression of Change (PGIC). At 4 weeks after administration of the third dose of study medicine, the fremanezumab monthly regimen produced favourable nominal differences for all outcomes. The lack of control of multiplicity for the comparisons of the two fremanezumab regimens with placebo for 7 different patient-reported outcomes should be noted.[3]

Two other randomised, double-blind, phase III studies demonstrated the superiority of both fremanezumab regimens over placebo in patients with episodic migraine (HALO EM[7]) and patients with chronic migraine (HALO CM[8]). The primary outcome of HALO-CM and HALO-EM were monthly average number of headache days of at least moderate severity, and monthly average number of migraine days, respectively. These studies were used to support the application for marketing authorisation for fremanezumab. However, they do not provide evidence to support the efficacy and safety of fremanezumab in the positioning proposed by the company.[1 2, 7, 8] The HALO extension study (n=1,889) was a long-term safety and tolerability study that included patients who completed the HALO-CM and HALO-EM studies, and an additional group who had not participated in HALO-CM or HALO-EM. The improvements from baseline in monthly average number of migraine days was maintained in patients with chronic and episodic migraine who continued on treatment from HALO-CM and HALO-EM until the end of the extension study, a total duration of up to 15 months.[2]

The submitting company presented a Bayesian network meta-analysis (NMA) comparing fremanezumab with botulinum toxin A in patients with chronic migraine who had been treated with three or more prior migraine preventive therapies. The NMA included data for fremanezumab, erenumab, and botulinum toxin A from four studies. The outcomes reported were the reduction in monthly migraine days and the proportion of patients with a ≥50% reduction in monthly migraine days. The credible intervals for the comparisons of fremanezumab against botulinum toxin A for both outcomes were very wide and included the threshold of likely no difference between treatments. The results of a sensitivity analysis, where erenumab study data were removed, were consistent with those from the full network.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The adverse event profile of fremanezumab in FOCUS is broadly in-line with the profile reported in HALO-EM and HALO-CM. Fremanezumab was generally well-tolerated in patients with episodic and chronic migraine. Injection-site reaction was the most commonly reported adverse event.[2, 3] The safety analysis for the FOCUS study was conducted in all randomised patients (with episodic and chronic migraine) who received at least one dose of study treatment. The proportions of patients in the fremanezumab monthly (n=285), fremanezumab quarterly (n=276) and placebo (n=277) groups with at least one treatment-related adverse event were 19%, 21% and 20%, with a serious adverse event were 1.4%, 0.7% and 1.4% and with adverse events leading to treatment discontinuation were 1.4%, 0.3% and 1.1%. No individual adverse event led to treatment discontinuation in more than one patient.[3] The most commonly reported adverse events in the fremanezumab monthly, fremanezumab quarterly and placebo groups were injection-site erythema (5.6%, 6.9%, 5.4%), injection-site induration (4.6%, 4.3%, 4.3%), injection-site pain (3.2%, 4.0%, 2.9%), nasopharyngitis (2.5%, 4.7%, 4.0), fatigue (3.2%, 3.3%, 1.1%) and upper respiratory tract infections (3.2%, 1.4%, 1.1%).[3]

There is concern that there may be an small but increased risk of vascular events such as myocardial infarction, ischaemic stroke and hypertensive crisis, in patients treated with fremanezumab.[2]

Summary of clinical effectiveness issues

Migraine is a neurological disorder characterised by disabling attacks of moderate to severe throbbing headache, which can be associated with nausea, vomiting, photophobia and phonophobia. Migraines can be classified as episodic or chronic based on the number of headache days/months: <15 days/month or ≥15 days/month respectively.[2, 9] Prophylactic treatment options for patients with episodic or chronic migraine include propranolol, topiramate, amitriptyline, candesartan (off-label), flunarizine (unlicensed calcium channel blocker), and sodium valproate (off-label). The tolerability issues, titration schedules and delayed onset of efficacy with some of these treatment options may reduce compliance and treatment effectiveness.[10] Botulinum toxin A (SMC 692/11) and erenumab (SMC2134) have been accepted by SMC for the prophylactic treatment of patients with chronic migraine who have been previously treated with three or more migraine prophylactic treatments.[10] Patients with episodic migraine who have not had an adequate response to three prior preventive treatments may receive acute migraine treatments and best supportive care.

The submitting company has requested that SMC considers fremanezumab when positioned for use in patients with chronic and episodic migraine who have had three or more prior migraine preventive treatment failures. Clinical experts consulted by SMC considered that fremanezumab fills an unmet need for the treatment of patients who have not benefited from other migraine preventive medicines.

The FOCUS study demonstrated superiority of both the monthly and quarterly regimens of fremanezumab over placebo for reducing the mean number of monthly migraine days in patients with chronic and episodic migraine previously treated with two to four preventive migraine medicines.[3] These reductions of 3 to 4 migraine days/month are likely to be meaningful to patients. Secondary outcomes and exploratory patient-reported outcomes on HRQoL were supportive of the primary outcome.

No direct comparison with an active treatment was presented. The relevant population for this submission was a subgroup of the overall FOCUS study population which was further divided into chronic and episodic patients. The study was not powered to detect statistical differences in these subgroups. Additionally, the subgroup analyses were conducted post-hoc without control for multiplicity.

There is a lack of comparative data to support fremanezumab use beyond 12 weeks and the lack of long-term comparative data is a limitation of the evidence presented.

The exclusion of patients with continuous or almost continuous headache, cardiovascular risk factors, major comorbidities and older patients may limit the generalisability of FOCUS efficacy results and may underestimate adverse event rates.[2, 3] For the treatment of chronic migraine the regimens with and without a loading dose of 675mg were considered to be equivalent by the European Medicines Agency, and the simplified regimen without the loading dose was considered likely to reduce the risk of dosing errors.[2]

The NMA comparing fremanezumab with botulinum toxin A had a number of limitations: the NMA was conducted using post hoc subgroup analyses of patients drawn from placebo-controlled studies. There was heterogeneity in the time-points at which the outcomes of the individual studies were reported and one of the comparisons compared different outcome measures (≥50% reduction in mean monthly migraine days with ≥50% reduction in mean monthly headache days) which increases uncertainty in the results of the analysis. There was also heterogeneity in the results reported for the control groups (placebo). This variation may in part be explained by differences in the placebo treatments (31 to 39 intramuscular injections to the neck and head every 12 weeks versus 1 to 3 subcutaneous injections monthly); eligibility criteria; and possibly differences in baseline characteristics because these data were not available for the relevant subgroup of patients from the botulinum toxin A studies. The analyses did not assess long-term efficacy, safety, and health-related quality of life, which may be clinically relevant when considering the risk/benefit of treatments and the long term variability of symptom frequency and severity. The credible intervals around the central estimates of relative effect were very wide and there is a lack of evidence to make any statement about the relative efficacy of fremanezumab with botulinum toxin A.

Results from an NMA in patients with episodic migraine were included in the economic analysis for the episodic population but this NMA was not submitted to SMC for appraisal. It is unclear why an NMA was undertaken in the episodic population comparing fremanezumab with placebo (as a proxy for best supportive care) as the FOCUS study provides direct evidence for this comparison.

Clinical experts consulted by SMC considered that fremanezumab is a therapeutic advancement as it specifically targets migraine pathophysiology and is administered as monthly or quarterly subcutaneous injections. They also considered there would likely be an impact on local neurology services with the introduction of this medicine, in order to support initiation and monitoring of treatment.

*Other data were also assessed but remain confidential.**

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis (CUA) comparing fremanezumab versus best supportive care (BSC) for the treatment of adult patients who have failed three or more

preventive oral therapies with chronic migraine or episodic migraine, and also versus botulinum toxin A in patients with chronic migraine. SMC clinical expert feedback confirmed botulinum toxin A as a relevant comparator in the chronic migraine patient population, although fremanezumab could be used after botulinum toxin A, hence BSC is a relevant comparator for some patients.

The economic analysis used a semi-Markov model design with an initial element consisting of an assessment of response to treatment conducted at 12 weeks for fremanezumab and 24 weeks for botulinum toxin A (that is applying a negative stopping rule with response defined as ≥50% and ≥30% reduction in monthly migraine days for episodic and chronic migraine respectively). Within each response or non-response health state a probability distribution of monthly migraine days for 1 to 28 days was estimated. Patients with no response at this first assessment were assumed to discontinue treatment and receive BSC (that is only acute migraine medicines), whereas responders continued to receive treatment until discontinuation followed by BSC. A mean age of 42 years for episodic migraine and 41 years for chronic migraine were assumed for patients entering the model. A 28-day model cycle matching the fremanezumab clinical trials assessment period was adopted with a base case 10-year time horizon.

The key clinical data used in the economic analysis for fremanezumab were the patient level data for the sub-group of chronic migraine and episodic migraine patients who had received at least three prior therapies from the FOCUS study. These data were also used to estimate the baseline distribution of monthly migraine days for responders and non-responders with episodic and chronic migraine, and to statistically model the changes in the distribution of monthly migraine days associated with an estimated mean reduction in monthly migraine days for fremanezumab versus BSC (placebo as a proxy) for responder and non-responder episodic (1 to 14 day distributions) and chronic (15 to 28 days) migraine patients. Due to a lack of published data for botulinum toxin A®, the same distributions and monthly migraine days treatment effects in responders and non-responders as for fremanezumab were assumed.

The relative responder rates in episodic migraine (≥50% reduction in monthly migraine days) and chronic migraine (≥30% reduction in monthly migraine days) for fremanezumab, botulinum toxin A and BSC were derived from the NMA and applied to the monthly migraine day distributions estimated at the initial assessments. The NMA only provided estimates for botulinum toxin A for a ≥50% reduction in monthly migraine days hence the estimate for chronic migraine responders were derived by using the relative responder rate data for fremanezumab versus botulinum toxin A for a ≥50% reduction in monthly migraine days from the NMA and estimating the proportion who would be expected to achieve ≥30% reduction based on fremanezumab estimates for this outcome. Response rates associated with placebo/BSC at 12 weeks were derived from the placebo arms of studies included in the NMA. Long run discontinuation estimates were derived from the longer term HALO clinical studies for fremanezumab, with the same discontinuation rate assumed for botulinum toxin A.

The company also included a positive stopping rule whereby a response assessment is carried out each 12 months after the initial assessment, consisting of a 12-week treatment break for all

responding patients. Based on expert opinion, it was assumed 20% of patients would maintain response and not recommence treatment.

It was assumed in the base case that the estimated monthly migraine day distributions estimated at week 12 or 24 are maintained for the rest of the model time horizon on the grounds that efficacy of the treatments would not be expected to wane over time. Mortality was assumed at the general population rates, and adverse events were not explicitly considered in the model due to the favourable safety profile of fremanezumab.

Utility estimates across the monthly migraine day distributions were estimated via a mapping of the MSQoL collected in the FOCUS clinical study to the EQ 5D-3L using a published algorithm.[11] This was used in preference to EQ-5D data collected in the clinical study which was stated by the company to not appropriately reflect utilities associated with monthly migraine days due to the data being collected at a clinic visit when the patient is less likely to be experiencing a migraine day. The full study data were used to estimate utilities while on-treatment (using 4 and 12 week MSQ data) and off-treatment (using the baseline data). A beta regression model was used to estimate utilities for the distribution of on and off-treatment monthly migraine days from 0 to 28 days. Over the whole monthly migraine days distribution there were lower utilities while off treatment than while on active treatment.

Costs included medicine acquisition costs, medicine administration costs for botulinum toxin A (none assumed for fremanezumab, apart from an initial training cost to self-administer the subcutaneous injection), monitoring costs and hospital/general practitioner resource use associated with monthly migraine days distribution derived from a published study of the burden of migraine in Europe, supplemented by a NICE submission.[12, 13] Fremanezumab is available as a monthly or quarterly subcutaneous injection but with the same medicine price, hence the company pooled the clinical data for each dose based on the assumption of no difference in efficacy between the regimens.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation by NHS Scotland.

The base case cost-effectiveness results for episodic and chronic migraine patients respectively are presented in Table 2 and Table 3 below at PAS prices. Incremental costs were driven by higher medicine and monitoring costs for fremanezumab, slightly offset by lower estimated resource use costs versus BSC and botulinum toxin A and higher administration costs for botulinum toxin A. Quality-adjusted life year (QALY) gains in the economic analysis are driven by the better responder rates estimated for fremanezumab, which converts to better HRQoL outcomes also associated with the estimated higher utilities estimated for being on-treatment with any level of monthly migraine days versus off-treatment.

Table 2. Base case results in episodic migraine patients

	ICER (cost/QALY)
Fremanezumab versus BSC in EM (with PAS)	£10,300

BSC = best supportive care; EM = episodic migraine, ICER = incremental cost-effectiveness ratio, PAS = patient access scheme, QALY = quality adjusted life year

Table 3.Base case with PAS results in chronic migraine patients

	ICER (cost/QALY)
Fremanezumab versus BSC in CM	£8,824
Fremanezumab versus botulinum toxin A in CM	£10,627

BSC = best supportive care; CM = chronic migraine, ICER = incremental cost-effectiveness ratio, PAS = patient access scheme, QALY = quality adjusted life year

A subgroup analysis of the cost-effectiveness of fremanezumab versus BSC for patients who have failed three prior therapies with high-frequency episodic migraine (8 to 14 monthly migraine days) was also provided and demonstrated a lower incremental cost-effectiveness ratio (ICER) versus BSC (Table 4). One way sensitivity analysis demonstrated the results in both episodic and chronic migraine were most sensitive to varying the initial distribution of monthly migraine days. A range of scenario analyses were performed consisting of varying time horizon, including a waning of treatment effects over a 5 year, 10 year and lifetime horizon, including a treatment administration cost for fremanezumab, reducing the impact of the positive stopping rule to 10% or none applied, using a 50% monthly migraine day reduction threshold for responder in chronic migraine, and separating efficacy data for quarterly and monthly fremanezumab dosing schedules, and a scenario assuming a higher discontinuation rate for botulinum toxin A was also requested. The results across both patient populations were most impacted by the time horizon, and not applying a positive stopping rule (Table 4). Additional scenario analysis was requested an increase the botulinum toxin A responder rate in chronic migraine which increased the ICER (Table 4).

Table 4. Selected scenario analysis results with PAS

	Sub-group/scenario analysis	Episodic Migraine	Chronic Migraine (versus BSC)	Chronic Migraine (versus botulinum toxin A)
		ICER (PAS price)	ICER (PAS price)	ICER (PAS price)
1	High frequency episodic migraine subgroup	£8,973	N/A	N/A
2	5 year time horizon	£17,070	£14,693	£18,401
3	Lifetime horizon	£3,083	£2,782	£3,250
4	No positive stopping rule	£15,169	£12,829	£17,044

5	Applying 50% MMD reduction threshold for responder in chronic migraine	N/A	£7,931	£11,027
6	Responder rate for botulinum toxin A in chronic migraine increased	N/A	N/A	£21,779
7	Using the FOCUS study data for relative responder rates for fremanezumab versus BSC	£10,773	N/A	N/A
8	Applying one set of monthly migraine days utilities (no on- off-treatment distinction)	£10,820	£9,606	£11,915
9	Assuming a 5 year cut-off for treatment benefit for fremanezumab versus BSC	£10,647	£9,107	N/A
10	Utilities based on the EQ-5D data from FOCUS	£28,384	£17,908	£20,680

BSC = best supportive care; CM = chronic migraine, ICER = incremental cost-effectiveness ratio, MMD =- monthly migraine days, N/A = not applicable, PAS = patient access scheme.

The economic analysis was associated with a number of weaknesses and uncertainties:

- The indirect treatment comparison performed to compare fremanezumab with botulinum toxin A in chronic migraine patients has limitations as described in the above clinical sections of the Detailed Advice Document (DAD), and there is insufficient evidence from this to support the lower response rate estimated for botulinum toxin A which drives the fremanezumab relative treatment effect in the economic analysis. The economic model predicts QALY gains for fremanezumab over botulinum toxin A despite the findings of no differences in the NMA. If fremanezumab has no additional treatment benefit versus botulinum toxin A, then there would exist an incremental cost with no apparent QALY gain. The modelling of the probability distribution of monthly migraine days and the relationship with relative responder rate estimates derived from the NMA is complex, and associated with some uncertainty in the modelled relative effectiveness results.
- For the comparison with BSC in episodic migraine and in chronic migraine, there are also concerns over the reliability of the relative responder rates estimated from the NMA. The company stated that responder estimates in episodic migraine have been derived from an NMA in this specific population however, as noted in the clinical effectiveness section above, this NMA was not submitted as evidence for assessment. Nonetheless, the relative responder estimates derived from the FOCUS study are lower than from the NMA, and seem preferable to use in the base case. Applying the FOCUS derived responder rates for fremanezumab versus BSC resulted in a slightly increased ICER of £10,773/QALY (Table 4). Smaller differences in responder rates between fremanezumab and BSC in episodic migraine based on the NMA only has a minimal impact on the ICER. Whilst the company has explained this as being due to a small relative difference between responder rates for fremanezumab and BSC/placebo, the analysis is complex and lacks some transparency.
- The company states that the use of differential on and off treatment utilities reflects treated patients better quality of life compared to placebo/BSC for the same number of monthly migraine days, based on the FOCUS clinical trial data, with the difference in quality of life reflecting the additional benefits of migraine treatment not captured by monthly migraine

days, such as nausea, shorter recovery time after migraine, and reduced severity. As these additional benefits of active treatment are uncertain, a scenario analysis was requested using one set of utilities for the monthly migraine day distributions, which increased the ICERs for fremanezumab versus BSC by a moderate amount (Table 4 scenario 8).

- While the rationale for not using the EQ-5D data from the FOCUS study to derive the base case utility values was reasonable, a scenario analysis requesting application of the EQ-5D derived utilities directly from the FOCUS clinical study was requested to explore the impact this has on the results, which increased the ICERs as shown in table 4, scenario 10.
- There is uncertainty over the relevance and applicability of the positive stopping rule in clinical practice, with lack of clarity and uncertainty over the assumptions of 20% ceasing treatment after the treatment break; and the assumption of maintenance of treatment benefit in the rest is uncertain. The ICER is increased if the positive stopping rule is removed (Table 4 scenario 4).
- The economic analysis did not attempt to capture any potential patient benefits of flexible and simpler dosing compared to botulinum toxin A, which may provide a small utility gain for fremanezumab.

Despite these uncertainties and weaknesses, the economic case for fremanezumab was considered demonstrated.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from The Migraine Trust and the National Migraine Centre, both organisations are registered charities.

- The Migraine Trust has received 4.2% pharmaceutical company funding in the past two years, with none from the submitting company. The National Migraine Centre has received 3% pharmaceutical company funding in the past two years, with none from the submitting company.

- Migraine greatly impacts the day-to-day lives of people who live with the condition. The symptoms associated with migraine attacks are painful and debilitating. They include severe throbbing pain in the head, nausea and vomiting, and sensitivity to light, sound and smell. One of the biggest challenges of living with migraine is its unpredictability as an attack can occur at any time. People with migraine say it impacts their ability to work or progress in their career, to spend time with their family, to socialise with friends, and to live up to their full potential. It also has a significant detrimental impact on mental health and wellbeing.

- Many of the current prophylactic treatments for migraine are medicines that have been developed for other medical conditions and repurposed for migraine. They often have unwanted side effects and patients may be unable to tolerate them for long enough or at a high enough dose for the medicine to be effective. There is an unmet need for migraine patients who have failed three or more prior preventive therapies.

- Fremanezumab is a preventive treatment specifically developed for migraine. It is a targeted treatment which appears to be well tolerated and easy to use, with the potential for fewer GP/hospital appointments, fewer side effects and the opportunity for substantial improvement in patients' quality of life.

Additional information: guidelines and protocols

The European Headache Federation (EHF) guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention was published in 2019.[14] This guidance includes an assessment of eptinezumab, erenumab, fremanezumab, and galcanezumab however there was insufficient available evidence to enable GRADE (e Grading of Recommendation, Assessment, Development, and Evaluation) recommendations to be drawn. Therefore the recommendations are based on expert opinion. The most salient recommendations included in the guidance are:

- anti-CGRP monoclonal antibodies should be used in migraine patients who have failed at least 2 previous medical treatments or where there is a contraindication to the use of such treatments.
- the cessation of treatment with anti-CGRP monoclonal antibodies should be considered after 6 to 12 months of treatment.[14]

The Scottish Intercollegiate Guidelines Network (SIGN) published Pharmacological management of migraine; A national clinical guideline (SIGN 155) in February 2018.[10] For the prevention of migraine, this guideline recommends propranolol as a first-line prophylactic treatment for patients with episodic or chronic migraine. Other recommended treatment options to be considered for prophylaxis in patients with episodic or chronic migraine include topiramate, amitriptyline, candesartan, and sodium valproate. Botulinum toxin A is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments. The guidance also acknowledges that pizotifen is widely used in clinical practice but that there is a paucity of available evidence.

Additional information: comparators

Botulinum toxin A and erenumab.

Cost of relevant comparators

Medicine	Dose Regimen	Cost year (£)
fremanezumab	**225mg subcutaneously once a month, alternatively 675mg subcutaneously every 3 months**	**5,400**
erenumab	70mg to 140mg subcutaneously every 4 weeks	5,024
botulinum toxin type A	155 to 195 units intramuscularly every 12 weeks	1,380

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 4 October 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 13,886 episodic migraine patients eligible for treatment each year, with 42 patients treated in year 1 rising to 181 patients treated in year 5 based on estimated uptake rates of 0.30% (year 1) rising to 1.30% (year 5). For the chronic migraine population, the company estimated there would be 6,527 patients eligible for treatment with fremanezumab each year, with 98 patients treated in year 1 rising to 424 patients treated in year 5 based on estimated uptake rates of 1.5% (year 1) rising to 6.5% (year 5).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 November 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.