Cost effectiveness of fremanezumab (Ajovy®) for the prophylaxis of migraine in adults who have at least four migraine days per month

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of fremanezumab in patients who have failed three or more migraine-preventive treatments. The NCPE recommends that, for chronic migraine, fremanezumab be considered for reimbursement. Also, the NCPE recommends that, for episodic migraine, reimbursement of fremanezumab be considered if cost effectiveness can be improved relative to existing treatments. These recommendations should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Teva Pharmaceuticals Ireland) dossier on fremanezumab. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits which the new treatment may provide and whether the cost requested by the company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **September 2020**

Summary

In September 2019, Teva Pharmaceuticals Ireland submitted a dossier on fremanezumab (Ajovy®) for the prophylaxis of migraine in adults who have at least four migraine days per month. Final correspondence from the Applicant was received in May 2020.

Cost effectiveness was evaluated in both the chronic migraine (CM) and episodic migraine (EM) settings. CM is defined as headache occurring on at least 15 days per month for three months (which on at least eight days per month has the features characteristic of migraine). EM is defined as headache occurring on less than 15 days per month. In the original submission, the Applicant evaluated cost effectiveness in patients who had failed two or more migraine-preventive treatments. The Irish College of General Practitioners Guidelines (2019) recommend that patients should have failed three or more migraine-preventive treatments before referral to a hospital-based specialist. Treatment with fremanezumab will require referral to a hospital-based specialist. On request, the Applicant updated the submission to investigate cost effectiveness in patients who have previously failed three or more migraine-preventive treatments. This population is a subgroup of the licensed population.

Fremanezumab is the third calcitonin gene-related peptide (CGRP) inhibitor to be approved by the EMA. It is formulated as a 225mg per 1.5ml solution for subcutaneous injection and is available as a pre-filled syringe. There are two licensed dosing regimens: 225mg once every month or 675mg once every three months. Reimbursement is sought under the High Tech Drug Arrangement.

The base case comparator is best supportive care (BSC). Erenumab and onabotulinumtoxinA were considered to be scenario comparators. As there is no direct evidence comparing treatment efficacy of fremanezumab with the scenario comparators, the Applicant conducted a series of network meta-analyses (NMAs). However, only the results of a secondary efficacy endpoint were used to inform the scenario comparator arms of the economic model. Equivalence assumptions were made for the primary efficacy endpoint. The Review Group does not consider these comparisons to be valid; cost effectiveness outputs are not reported here.

1. Comparative effectiveness of fremanezumab

Clinical trial evidence was derived from three phase-III, double-blind, placebo-controlled, parallel-group, randomised controlled pivotal trials: HALO-CM (n=1,130), HALO-EM (n= 875) and FOCUS (n=838). Patients with CM were recruited to HALO-CM; patients with EM were recruited to HALO-EM. FOCUS recruited both patients with CM and EM; randomisation was stratified accordingly. Both HALO trials included patients who had failed a maximum of two migraine-preventive treatments. FOCUS included patients who had failed two to four classes of migraine-preventive treatments; 50% of patients recruited to FOCUS had failed three or more migraine-preventive treatments. Patients were randomised 1:1:1 to receive fremanezumab 675mg once every three months, fremanezumab 225mg once every month, or placebo. Patients with CM (HALO-CM and FOCUS), who were assigned to fremanezumab 225mg once every month, received a 675mg loading dose at baseline. Outcomes of the trials included mean change in the average number of monthly headache days, and in the average number of monthly migraine days (MMDs). Headache day was defined as a day in which headache pain lasted at least four consecutive hours and had a peak severity of at least moderate level, or a day in which acute migraine-specific medication was used to treat a headache of any severity or duration. In HALO-CM and FOCUS, migraine day was defined in the same way as headache day with the exception that headache pain was required to meet criteria for migraine or probable migraine. In HALO-EM, the definition of a migraine day differed from that used in HALO-CM and FOCUS in that patients were required to experience two consecutive hours of headache pain meeting criteria for migraine or probable migraine. The Review Group noted that a considerable placebo effect was demonstrated across all three trials.

In HALO-CM, the mean change in the average number of monthly headache days (primary endpoint) was -4.3 (95% CI -4.9 to -3.7) with fremanezumab once every three months, -4.6 (95% CI -5.2 to -4.0) with fremanezumab once every month, and -2.5 (95% CI -3.1 to -1.9) with placebo; $p<0.0001$ for all comparisons of fremanezumab with placebo. The mean change in the average number of MMDs (secondary endpoint) was -4.9 (95% CI -5.6 to -4.2) with fremanezumab once every three months, -5.0 (95% CI -5.7 to -4.3) with fremanezumab once every month and -3.2 (95% CI -3.9 to -2.5) with placebo; $p<0.0001$ for all comparisons of fremanezumab with placebo. The proportions of patients achieving ≥50% reduction in the

average number of headache days per month (secondary endpoint) were 38%, 41% and 18% respectively.

In HALO-EM, the mean change in the average number of MMDs (primary endpoint) was -3.4 (95% CI -3.9 to -3.0) with fremanezumab once every three months, -3.7 (95% CI -4.2 to -3.2) with fremanezumab once every month, and -2.2 (95% CI -2.7 to -1.7) with placebo; p<0.001 for all comparisons of fremanezumab with placebo. The proportions of patients achieving ≥50% reduction in the average number of MMDs (secondary endpoint) were 44%, 48% and 28%, respectively.

In FOCUS, the mean change in the average number of MMDs (primary endpoint) was -3.7 (95% CI -4.4 to -3.1) with fremanezumab once every three months, -4.1 (95% CI -4.7 to -3.4) with fremanezumab once every month, and -0.6 (95% CI -1.3 to 0.1) with placebo. The proportions of patients achieving ≥50% reduction in the average number of MMDs (secondary endpoint) were 34%, 34% and 9%, respectively. Both dosing regimens of fremanezumab demonstrated consistently favourable improvements in health related quality of life (HRQoL) outcomes (secondary endpoint) compared to placebo. Tools used to measure HRQoL included Migraine Specific Quality of Life (MSQoL) score, Headache Impact Test and Migraine Disability Assessment. Subgroup analysis of the primary endpoint was conducted for CM and EM. The mean change in the average number of MMDs for patients with CM was -3.9 (95% CI -4.8 to -3.0) with fremanezumab once every three months, -4.5 (95% CI -5.4 to -3.6) with fremanezumab once every month, and -0.7 (95% CI -1.6 to 0.2) with placebo; p<0.0001 for all comparisons of fremanezumab with placebo. The mean change in the average number of MMDs for patients with EM was -3.7 (95% CI -4.6 to -2.8) with fremanezumab once every three months, -3.8 (95% CI -4.7 to -2.9) with fremanezumab once every month, and -0.7 (95% CI -1.5 to 0.19) with placebo; p<0.0001 for all comparisons of fremanezumab with placebo.

Patients who completed HALO-CM and HALO-EM were eligible to participate in the HALO extension study. Over 1,400 patients rolled over and an additional 312 patients were recruited. There was no placebo control; patients and investigators were blinded to the fremanezumab schedule. At 12 months, reductions in mean MMDs were sustained with both fremanezumab once every month and fremanezumab once every three months. More than 50% of patients in each treatment arm achieved ≥50% reduction in MMDs at month 12.

2. Safety of fremanezumab

Over 2,500 patients were treated with fremanezumab in pivotal trials; over 1,400 received it for at least 12 months. The most commonly reported adverse drug reactions (ADRs) were local reactions at the injection site including pain (24%), induration (17%), erythema (16%) and pruritis (2%). Most were mild to moderate in severity with less than 4% of patients discontinuing treatment due to ADRs. There is a concern that CGRP inhibitors may negatively impact on cardiovascular safety. Patients with cardiovascular disease were excluded from the trials; there is no data regarding safety of fremanezumab in this group. Fremanezumab should be avoided in pregnancy, and there may be concerns regarding treatment in women of child-bearing age, in the absence of data. Two post-authorisation safety studies, investigating the safety of fremanezumab in these patient groups, are to be conducted as part of the Risk Management Plan recommended by the EMA.

3. Cost effectiveness of fremanezumab

Methods

Of note, the licensed indication of fremanezumab is for prophylaxis of migraine in adults who have at least four migraine days per month. Here, cost effectiveness is investigated in patients who have previously failed three or more migraine-preventive treatments. This population is a subgroup of the licensed population.

Cost effectiveness was evaluated in a state-transition semi-Markov model that included 28 discrete migraine-frequency health states. These states were defined in line with the MMD outcomes from FOCUS. The cycle length was 28-days; the horizon was lifetime.

Direct clinical evidence was derived from FOCUS. Treatment effect for fremanezumab was informed by a combined analysis of the efficacy outputs for the two regimens of fremanezumab (i.e. 225mg once every month and 675mg once every three months). The placebo arm (acute medication and healthcare resource) provided evidence for BSC alone. A reduction in MMD results in a reduction in the acute medication and resources associated with BSC. Patients in the fremanezumab arm are assumed to receive concurrent BSC.

The model assumes patients retain maximum treatment benefit (measured at week 12 in FOCUS) while on treatment. Data from the HALO extension study was presented as evidence. However, this study provides evidence only for up to about 2% of the modelled time horizon. In the model, patients could discontinue treatment due to non-responder identification at 12 weeks, negative discontinuation (due to adverse events or lessening efficacy), or positive discontinuation (following periodic evaluations of response to treatment removal). The Applicant's base case assumed that patients retain some or all of the treatment benefit following discontinuation for the remainder of the lifetime horizon. No evidence was provided to support this.

In the Applicant's base case, on and off-treatment utility values for each migraine-frequency health state were estimated using EQ-5D-3L data mapped from MSQoL data collected during FOCUS while patients received treatment and at baseline, respectively. These were applied to the fremanezumab and BSC arms respectively. The Review Group notes that the approach overestimates any HRQoL benefit fremanezumab may have over BSC; the application of baseline utility to the BSC arm does not account for a large placebo effect observed in the HRQoL data.

Results

As previously mentioned, cost effectiveness here is investigated in patients who have previously failed three or more migraine-preventive treatments. This population is a subgroup of the licensed population.

The NCPE adjusted base case comprised a number of modifications to the Applicant's base case. These modifications included adjustments to the loss of treatment benefit following positive or negative discontinuation, the use of treatment-indifferent migraine-frequency health state utility values, and the use of age-adjusted utilities.

The resultant incremental cost-effectiveness ratios (ICERs) for fremanezumab versus BSC are provided in Table 1 (a & b).

Table 1a: NCPE adjusted base case; Fremanezumab versus BSC

Population	Incremental Costs (€)	Incremental QALYs	ICER (€/QALY)
Chronic Migraine	9,672	0.41	23,745
Episodic Migraine	10,878	0.17	62,951

Table 1b: Applicant's base case; Fremanezumab versus BSC

Population	Incremental Costs (€)	Incremental QALYs	ICER (€/QALY)
Chronic Migraine	7,789	1.04	7,465
Episodic Migraine	8,056	0.93	8,658

Where: BSC=best supportive care; QALY=Quality adjusted life year; ICER =incremental cost-effectiveness ratio.

Note: Figures in the table are rounded, and so calculations will not be directly replicable.

Sensitivity analysis

Under the NCPE adjusted base case, the probabilities of cost effectiveness in the CM setting are 37.1% and 54.3% at the €20,000/QALY and €45,000/QALY willingness to pay thresholds, respectively. In the EM setting, the respective probabilities are 36.5% and 47.6%.

Given the limited supporting evidence and uncertainty associated with the assumption of continued lifetime benefit while on treatment, the Review Group applied 5 and 10-year treatment waning effects to the NCPE adjusted base case. The ICERs in the EM setting increased to €96,531/QALY and €77,913/QALY, respectively. The ICERs in the CM setting increased to €29,293/QALY and €26,533/QALY respectively. Thus, if future evidence were to demonstrate that some loss of benefit does occur over time, cost effectiveness will be substantially impacted. The EM setting is particularly sensitive to treatment waning.

4. Budget impact of fremanezumab (specifically include list price of drug and the price per patient per year (or per treatment course as applicable)

The price to wholesale for a single pre-filled syringe of fremanezumab (225mg per 1.5ml) is €535. The dosage regimens are 225mg once every month or 675mg once every three months. The total cost per patient per year to the HSE (incorporating rebate and pharmacy patient care fees) for the respective regimens is €8,919.59 and €8,671.48, including VAT. The budget impact analyses are based on the cost of the 225mg once every month regimen.

In order to derive the eligible population, the Applicant first considered patients with migraine who had failed two or more previous migraine-preventive treatments. The proportion of those patients likely to fail a third treatment (an estimate which was derived from clinical opinion) and the estimated market share value for fremanezumab were then consecutively applied. The Applicant estimated that 568 patients would receive fremanezumab in year one increasing to 1,564 by year five. The gross budget impact was estimated to be €5.1 million in year one increasing to €13.9 million by year five. The five-year cumulative gross budget impact is €49.6million. Given the low cost of BSC, the net budget impact is similar to the gross budget impact.

The Review Group considers that several assumptions made by the Applicant to estimate the eligible patient population are highly uncertain. The prevalence rate that was used to estimate the number of patients having failed two or more migraine-preventive treatments considered only patients currently prescribed migraine-preventive treatment; those no longer prescribed preventive therapy were not included. The Review Group has concerns that a consequence of this assumption may be an underestimation of the eligible patient population. The Review Group also considers there to be uncertainty with respect to the estimated proportion of patients likely to fail a third treatment, and to the estimated market share values.

5. State if any patient submissions were received, and name submitting organisations.

A patient organisation submission was received from the Migraine Association of Ireland.

6. Conclusion

Of note, all recommendations here pertain to a subgroup of the licensed population. The NCPE recommends that, if reimbursed, implementation of measures to manage access to fremanezumab should be considered.

The NCPE recommends that fremanezumab (Ajovy®), for the prophylaxis of migraine in adult patients with CM who have failed three or more migraine-preventive treatments, be considered for reimbursement. *

The NCPE recommends that fremanezumab (Ajovy®), for the prophylaxis of migraine in adult patients with EM who have failed three or more migraine-preventive treatments, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. *

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.