NICE National Institute for Health and Care Excellence

NICE guidance

Atogepant for preventing migraine

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Atogepant is recommended as an option for preventing migraine in adults who have at least 4 migraine days per month, only if at least 3 preventive medicines have failed.

1.2 Stop atogepant after 12 weeks if the frequency of migraines does not reduce by:

- at least 50% in episodic migraine (defined as fewer than 15 headache days per month)
- at least 30% in chronic migraine (defined as 15 or more headache days per month, with at least 8 of those having features of migraine).

1.3 If people with the condition and their healthcare professional consider atogepant to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take account of administration costs, dosage, price per dose and commercial arrangements.

1.4 This recommendation is not intended to affect treatment with atogepant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

For this evaluation, the company asked for atogepant to be considered only for people who have already had at least 3 preventive medicines that have not worked. This does not include everyone who atogepant is licensed for. Usual preventive medicines at this point include erenumab, fremanezumab, galcanezumab, eptinezumab, rimegepant (for episodic migraine only) or botulinum toxin type A (for chronic migraine only).

Clinical trial evidence shows that atogepant reduces monthly migraine days more than placebo, but there is no clinical trial evidence directly comparing it with other preventive medicines. The results from indirect comparisons are uncertain and it is unclear how well atogepant works compared with other preventive medicines for episodic or chronic

migraine.

For episodic migraine, the most relevant comparator is rimegepant because it is also an oral preventive medicine. The most likely cost-effectiveness estimate for atogepant compared with rimegepant is within the range that NICE normally considers an acceptable use of NHS resources.

For chronic migraine, it is not clear whether atogepant is better or worse than the other preventive medicines, but it has lower costs. So, atogepant is recommended for preventing episodic and chronic migraine after 3 or more preventive medicines.

2 Information about atogepant

Marketing authorisation indication

2.1 Atogepant (Aquipta, AbbVie) is indicated for 'prophylaxis of migraine in adults who have at least 4 migraine days per month'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for atogepant.

Price

2.3 The list price of atogepant is £182.16 for 28 tablets (excluding VAT; company information).

2.4 Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The evaluation committee considered evidence submitted by AbbVie, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Migraine attacks usually last between 4 hours and 72 hours. They involve throbbing head pain of moderate-to-severe intensity, which can be highly disabling, impacting mental wellbeing and physical activities. Migraine can be classified as episodic or chronic, based on the frequency of headaches. Episodic migraine is defined as fewer than 15 headache days per month. Chronic migraine is defined as 15 or more headache days per month with at least 8 of those having features of migraine. The committee concluded that migraine is a debilitating condition that substantially affects physical, social, psychological, and professional aspects of life.

Clinical management

Treatment options

3.2 People with at least 4 migraine days per month are offered a range of oral preventive medicines, including topiramate, propranolol and amitriptyline. If 3 of these have not worked or cannot be tolerated, people can have erenumab, fremanezumab, galcanezumab or eptinezumab as fourth-line treatments. These drugs are injectable anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies. People with episodic migraine can have the oral preventive medicine rimegepant, and people with chronic migraine can have botulinum toxin type A, which is an intramuscular preventive medicine. Patient experts explained that some people cannot have injectable medicines, for example because they have

an allergy or phobia of needles. So people with migraines would welcome an oral medicine, particularly for chronic migraine for which no other oral medicine is available. A clinical expert also explained that the half-life of atogepant is shorter than that of the injectable medicines. Therefore, it would be beneficial for people who may need to stop the treatment quickly, such as people with high vascular risk or people considering conception. The committee concluded that there was an unmet need for new preventive treatment options.

Comparators

3.3 Clinical experts explained that eptinezumab is given by intravenous infusion in hospital and so its use in clinical practice is limited by capacity issues. They also explained that use of botulinum toxin type A is not consistent across the country and depends on the availability of specialist staff. The company considered that eptinezumab and botulinum toxin type A were not relevant comparators. It also considered that rimegepant was not a relevant comparator because it had only recently been recommended by NICE and was not yet established practice in the NHS. The committee considered that, although use may vary between centres, the following medicines are available in clinics where atogepant would be available and so are relevant comparators:

- erenumab
- fremanezumab
- galcanezumab
- eptinezumab
- rimegepant, and
- botulinum toxin type A.

The committee considered that use of rimegepant would likely increase and that for episodic migraine, it was the most relevant comparator for atogepant because it is also an oral medicine.

Setting

3.4 The company initially positioned atogepant as being started in secondary care and agreed a commercial arrangement that limited prescribing of atogepant to secondary care. But, it stated that there was potential for it to be monitored in primary care and for follow-up appointments to be done by GPs. Patient and professional organisations stated that availability of atogepant in primary care would improve access to treatment and reduce costs to the NHS. The committee considered that atogepant would initially be prescribed and monitored in secondary care, but that there would be interest in being able to use it in primary care. After the committee meeting, the company removed the commercial arrangement, so atogepant can be used in all applicable settings.

Clinical effectiveness

Clinical trials

3.5 The company's evidence for atogepant came from 2 clinical trials:

- ELEVATE, which compared atogepant with placebo in adults with episodic migraine when 2 to 4 preventive medicines had failed, and
- PROGRESS, which compared atogepant with placebo in adults with chronic migraine who had already had up to 4 preventive medicines.

The EAG considered that 2 other trials comparing atogepant with placebo also provided relevant data. They were:

- CGP-MD-01, which included adults with episodic migraine when up to 2 preventive medicines had failed, and
- ADVANCE, which included adults with episodic migraine when up to 4 preventive medicines had failed.

The primary outcome in the trials was the change from baseline in monthly migraine days (MMDs). Secondary outcomes included the proportion of people achieving at least a 50% reduction in mean MMDs, the proportion

achieving at least a 30% reduction in mean MMDs (chronic migraine only) and change from baseline in acute medicine-use days. The results from ELEVATE are confidential and cannot be reported here. For episodic migraine, the change from baseline in MMDs was significantly greater with atogepant than placebo (mean difference −0.70 days in CGP-MD-01 and −1.7 days in ADVANCE). For chronic migraine in PROGRESS, the change from baseline in MMDs was significantly greater with atogepant than placebo (mean difference −1.82). Results from the secondary outcomes also suggested atogepant was more effective than placebo. ELEVATE and PROGRESS reported results for the subgroup of people when 3 preventive medicines had failed. This was the subgroup relevant to the decision problem for this evaluation, but the results are confidential and cannot be reported here. In the subgroup in ELEVATE, the change from baseline in mean MMDs was greater with atogepant than placebo. The committee noted that PROGRESS had not been powered to assess the treatment effect in this subgroup and that the number of people included was small. The committee concluded that atogepant was more effective than placebo in preventing episodic and chronic migraine in the overall population. But for people with chronic migraine who have tried 3 preventive medicines that have failed, the efficacy of atogepant was uncertain.

Network meta-analysis

3.6 There is no evidence that directly compares atogepant with any of the relevant comparators. So the company did several network meta-analyses to estimate the relative effect of atogepant for the MMD-based outcomes, all-cause discontinuation, health-related quality of life and adverse events. The results from the network meta-analyses for the MMD-based outcomes and all-cause discontinuation were used in the economic model. The company included data from separate clinical trials of atogepant, erenumab, galcanezumab, fremanezumab and botulinum toxin type A (although the company did not consider it a relevant comparator). The company's network meta-analyses included 16 studies for episodic migraine and 10 for chronic migraine. For the MMD-related outcomes in episodic migraine, the company included data from the subgroup of people for whom 3 preventive medicines had failed, because ELEVATE was stratified for this subgroup. For chronic migraine, the company

included the overall population from the trials. The EAG considered that rimegepant and eptinezumab were also relevant comparators and expanded the network meta-analyses to include data for these medicines. The EAG highlighted that although ELEVATE was stratified for the subgroup, the comparator trials were not. It noted that there was limited data for the subgroup and some of the company's network meta-analysis models for the subgroup did not converge. The EAG's clinical experts stated that there were no concerning differences between the baseline characteristics of the overall population and the subgroup. So, the EAG preferred to use data for the overall population for episodic migraine as well as for chronic migraine to reduce uncertainty in the results. At the committee meeting, the company agreed with the EAG that using data for the overall population for the network meta-analyses in episodic migraine improved the reliability of the analyses. The company explored random- and fixed-effects models for the network meta-analyses, and also explored adjusting for the differing placebo effects observed in the included trials. It considered that the random effects analyses were appropriate because there was heterogeneity across the trials. It also considered that adjusting did not substantially improve the model fit, and so it used unadjusted models for all outcomes. The EAG preferred adjusted models, which in most cases reduced between-study heterogeneity. The results of the network meta-analyses are confidential and cannot be reported here. The committee noted that the differences between medicines were small for all outcomes, and that for most results, the credible intervals included the null effect. It noted that for the company's network meta-analyses, some of the credible intervals were extremely wide and so considered that the results were not reliable. The committee considered that the subgroup of people for whom 3 preventive medicines had failed was in line with the decision problem. Its preference was therefore for the network meta-analyses to be conducted in this subgroup. But, it considered the EAG's concerns and the large uncertainty in the company's results in the subgroup for episodic migraine. It concluded therefore that it was acceptable to consider the results in the overall population in both episodic and chronic migraine. The committee agreed with the EAG that adjusting for placebo effect was preferable, where possible. The committee concluded that the results of the network meta-analysis were uncertain and did not provide clear evidence that atogepant was better or worse than any comparator for episodic or chronic migraine.

Economic model

Company's model

3.7 The company presented a semi-Markov state transition model. In the model, response was assessed at 12 weeks (24 weeks for botulinum toxin type A) after the start of treatment. After the assessment, people who had a response continued with treatment, and those who had no response stopped. People could also stop treatment before or after the assessment, regardless of response. All costs and quality-adjusted life years (QALYs) within each health state were based on MMD distribution. The committee concluded that the company's model was appropriate for decision making.

Monitoring costs

3.8 The company used healthcare resource-use data from the NICE technology appraisal guidance on erenumab. The data was originally sourced from the National Health and Wellness Survey and mapped to the number of MMDs, and included neurologist and GP visits. The company also included additional monitoring costs, which assumed some monitoring would be done in primary care for atogepant, while all follow up for CGRP monoclonal antibodies would be in secondary care. The EAG removed the additional monitoring costs because it considered them to be double counting and noted that additional costs had not been included in previous migraine evaluations. At the committee meeting, the company agreed with the EAG that the additional monitoring costs should be removed. The committee concluded that the additional monitoring costs should not be included in the model.

Injection-related disutility

3.9 The company included a disutility assumption in the model for subcutaneous injections based on a paper by Matza et al. (2019). The EAG noted that the utility difference between 1 injection per month and oral medicine in the paper was not significant and it was not based on EQ-5D. A disutility for injection had also not

been included in the rimegepant evaluation. So the EAG removed the disutility assumption in its preferred base-case model. The patient and clinical experts explained that people with migraine are more concerned about the efficacy of a medicine than the method of administration, so it was unlikely that people would decline an injectable medicine. The committee agreed that although there may be differences in patient preference for oral or injectable medicines and that an oral medicine could provide benefits for some, it was not appropriate to include the injection-related disutility from Matza et al. (2019) in the model.

Mean responder MMDs

3.10 The company included a restriction in the model so that responder MMDs could not fall below 1, to prevent clinically implausible MMD results arising from the network meta-analysis. The EAG agreed that negative MMDs were implausible but considered that values between 0 and 1 were plausible, so the EAG set the restriction at 0. The EAG also noted that when using the EAG's preferred network meta-analysis results, the restriction had very little impact. At the committee meeting, the company explained that the restriction was a mean value, so if the restriction was set at 1 some people could still have fewer than 1 MMDs. The committee concluded that it was acceptable to restrict mean responder MMDs to 1 but noted that it had little impact when using the EAG-preferred network meta-analysis results.

Long-term discontinuation

3.11 The company included a discontinuation rate of 3.59% per cycle for all active treatments. This was based on the LTS-302 study, which was a long-term safety and tolerability study of atogepant in episodic migraine. The EAG identified an error in the company's calculation, and so preferred to use a rate of 0.44%, which was included in one of the company's scenario analyses and was taken from the NICE technology appraisal guidance on galcanezumab. The EAG also noted that the discontinuation rate in the NICE technology appraisal guidance on erenumab was 2.38%. At the committee meeting, the company stated that it had obtained further data from the LTS-302 study and calculated an updated discontinuation rate, which it considered to be confidential. The EAG suggested some changes to

the company's calculation and also produced an updated rate. The committee agreed that it was appropriate to use a long-term discontinuation rate that had been calculated from a study of atogepant. So it concluded that the EAG's updated rate should be used in the model.

Acceptable ICER

3.12 NICE's manual for health technology evaluations notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, decisions about the acceptability of a technology as an effective use of NHS resources will consider the degree of uncertainty around the ICER. The committee considered that there was a very high level of uncertainty in the clinical evidence included in the model. This was because the network meta-analyses were not based on the population covered by the decision problem and the credible intervals were very wide (see section 3.6). The committee also considered that the impact on NHS resources could be high because migraine is a common condition. So it considered that an acceptable ICER for atogepant would be around £20,000 per QALY gained.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.13 The company and EAG base cases differed in the following 5 key ways:

- In the network meta-analyses (see section 3.6), the company's analysis used the subgroup population for episodic migraine and used random effects, unadjusted models for all outcomes. The EAG expanded the network meta-analysis to include rimegepant and eptinezumab, used the overall population for both episodic and chronic migraine and used alternative models, including adjusting for the placebo effect where possible.
- Mean responder MMDs (see section 3.10) were restricted to 1 in the company's model and to 0 in the EAG's.

- The company used a long-term discontinuation rate of 3.59% per cycle and the EAG used a rate of 0.44% per cycle (see section 3.11). The company provided an updated discontinuation rate after the committee meeting, which the EAG amended.
- The company included additional monitoring costs and the EAG did not (see section 3.8).
- The company included an injection-related disutility for the CGRP monoclonal antibody medicines and the EAG did not (see section 3.9).

The committee agreed that its preferred assumptions were those in the EAG base case, except it preferred to restrict mean responder MMDs to 1 and to use the EAG's updated long-term discontinuation rate. There were confidential discounts for some of the comparators, so some of the exact cost-effectiveness estimates are confidential and cannot be reported here. The committee noted that the incremental QALYs gained were very small and recalled that there was a high level of uncertainty in the results of the network meta-analyses. It considered that it was unclear whether atogepant was better or worse than the comparators, and also took the incremental costs into account in its decision making. The committee also noted that the net health benefit at a threshold value of £20,000 per QALY was sometimes positive and sometimes negative, depending on the comparator. In episodic migraine, the ICER compared with rimegepant was £20,000 per QALY for the committee's preferred scenario and the committee recalled that it had considered rimegepant to be the most relevant comparator for atogepant (see section 3.3). In the committee's preferred scenario in chronic migraine, atogepant was dominant (more effective and less costly) compared with 3 of the comparators. Compared with the 3 remaining comparators, the costs with atogepant were lower.

Other factors

Equality

3.14 Patient and professional organisations highlighted that migraine is more common

in women than in men. The committee agreed that issues relating to differences in prevalence or incidence of a condition cannot be addressed in a technology evaluation. A stakeholder commented that an oral medicine would benefit people who cannot self-administer an injectable medicine because of disability. The committee considered that atogepant could improve access to specialist treatment for people with difficulty self-injecting the CGRP monoclonal antibodies administered subcutaneously. The committee agreed that there were no equality issues relevant to the recommendations.

Severity

3.15 NICE's advice about conditions with a high degree of severity did not apply.

Conclusion

Recommendation

3.16 The committee concluded that in episodic migraine, the most likely cost-effectiveness estimate for atogepant compared with rimegepant was within the range that the committee considered to be an acceptable use of NHS resources. In chronic migraine, the costs with atogepant were lower than those of all the comparators. So, the committee recommended atogepant for preventing both episodic and chronic migraine in adults. The committee agreed that atogepant should be stopped after 12 weeks if the frequency of migraine does not reduce by:

- at least 50% in episodic migraine, and
- at least 30% in chronic migraine.

This reflects the clinical trials and current clinical practice. Also, the committee agreed that, after people with the condition and their clinicians have discussed the advantages and disadvantages of the available medicines, taking into account the administration costs, dosage, price per dose and commercial arrangements, if more than 1 treatment is suitable, it

would be appropriate to choose the least expensive option.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has episodic or chronic migraine and the healthcare professional responsible for their care thinks that atogepant is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel
Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Kirsty Pitt
Technical lead

Caron Jones
Technical adviser

Celia Mayers
Project manager

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