NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Efgartigimod for treating generalised myasthenia gravis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using efgartigimod in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on efgartigimod. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using efgartigimod in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 22 September 2023
- Second evaluation committee meeting: 16 November 2023
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Efgartigimod is not recommended, within its marketing authorisation, as an add-on to standard treatment for generalised myasthenia gravis in adults who test positive for anti-acetylcholine receptor antibodies.

1.2 This recommendation is not intended to affect treatment with efgartigimod 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 clinician consider it appropriate to stop.

Why the committee made these recommendations

Standard treatment for generalised myasthenia gravis in adults who test positive for anti-acetylcholine receptor antibodies includes surgery, acetylcholinesterase inhibitors or immunosuppressants. Efgartigimod would be used as an add-on to standard treatment.

Clinical trial evidence suggests that efgartigimod plus standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone. But it is uncertain if the people in the trial reflect the people who would have efgartigimod in the NHS.

There are also uncertainties in the economic model that make the likely cost-effectiveness estimates for efgartigimod uncertain. The most likely cost-effectiveness estimates are above what NICE considers an acceptable use of NHS resources. So, efgartigimod is not recommended.

2 Information about efgartigimod

Marketing authorisation indication

2.1 Efgartigimod (Vyvgart, Argenx) is indicated as 'an add-on to standard therapy for the treatment of adult patients with generalised Myasthenia

Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of efgartigimod is £6,569.73 per 400-mg vial (excluding VAT, company submission).

2.4 The company has a commercial arrangement, which would have applied if efgartigimod had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Argenx, 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

3.1 Myasthenia gravis is an autoimmune condition that can affect multiple muscle groups, and causes muscle weakness and fatigue. At first, it usually only affects the eye muscles. But, in around 80% of people, it will affect other muscle groups and become generalised myasthenia gravis (gMG). Most people with gMG have anti-acetylcholine receptor (AChR) antibodies. The patient experts explained that symptoms of gMG can vary and that their impact can also change from day to day. They explained the condition can have substantial physical, emotional, and financial impacts on the person with gMG, as well as their family. There is currently no cure for gMG. The patient experts noted that treatments for gMG are associated with side effects that need managing and that there is a high unmet need for effective treatments. They explained that many people with gMG have corticosteroids, but finding a dose that manages

symptoms while minimising the risk of side effects is challenging. They also said that strict treatment schedules can impact daily life and that managing these and side effects of multiple treatments together is difficult. The patient experts explained that people with gMG spend their life fearing a myasthenic crisis. Myasthenic crisis is the most common cause of gMG-related deaths and occurs when the muscles that control breathing stop working. The committee concluded that gMG is a debilitating condition with a high treatment burden.

Clinical management

Treatment options

3.2 gMG is a chronic condition and most people need lifelong treatment. The clinical experts explained that people would usually have treatments outlined in the Association of British Neurologists (ABN) guidelines. But they added that, at the time of this evaluation, the ABN guidelines are being updated. The ABN (2015) guidelines recommend that people are first offered pyridostigmine at the lowest effective dose and that surgery to remove the thymus gland can be considered for people under 45 years. If symptoms continue, people should be offered prednisolone. The clinical experts explained that corticosteroids like prednisolone are associated with notable side effects and that they aim to use minimal doses to minimise side effects. The ABN guidelines recommend that people are offered a non-steroidal immunosuppressive agent such as azathioprine if remission is not achieved on corticosteroids alone. If their condition does not respond to immunosuppressants or they experience notable side effects on increasing corticosteroid doses, expert advice should be sought on the use of plasma exchange or intravenous immunoglobulin (IVIg). The NHS England commissioning criteria policy for the use of therapeutic immunoglobulin recommends IVIg should be used:

- when urgent inpatient treatment is needed and plasma exchange is not available

- in rare circumstances as a maintenance treatment when all standard treatments have failed and the person is having treatment in a specialist neuromuscular service.

NHS England considers rituximab, an anti-B-cell monoclonal antibody treatment, to be an equally effective treatment to IVIg. It has stated that rituximab should be considered for several populations. The patient experts explained that existing treatments are not only associated with notable side effects but can be slow to take effect. The committee concluded that an effective and fast-acting treatment option would be welcomed by people with gMG and clinicians.

Population

3.3 Efgartigimod has a marketing authorisation as an add-on to standard treatment for gMG. The company positioned efgartigimod as a treatment for gMG in people with uncontrolled symptoms despite established clinical management. The clinical experts considered that efgartigimod could be positioned at several points in the clinical pathway. They added that, initially, it would be used in specialist centres for gMG in people with substantial symptoms despite optimal standard treatment. But, they also explained that, in time, the treatment could be used in additional populations, including the much larger population whose symptoms remain sub-optimally controlled despite established clinical management. The clinical experts explained that this is because gMG becomes more severe over time and so they aim to use the most effective treatments as early as possible. They stated that efgartigimod could also potentially reduce the corticosteroid dose needed. The committee noted that the marketing authorisation indication for efgartigimod positions it at any point after standard therapy has been started. The committee also noted that the company used efficacy data from the ADAPT trial in its model (see section 3.5). The committee considered that the inclusion criteria for ADAPT may not reflect the population that could have efgartigimod in NHS clinical practice if it was recommended within its marketing

authorisation. The committee highlighted that the clinical and cost effectiveness of efgartigimod would change for different populations. It concluded that further input from clinical experts to help define a population in which efgartigimod is both clinically and cost effective is needed. It considered that the characteristics of this population should be clearly defined to enable use in the NHS.

Maintenance IVIg

3.4 The company considered that maintenance IVIg is part of established clinical management in the NHS and that it is received by a notable proportion of the people who would be offered efgartigimod. The EAG explained that it had received clinical advice that IVIg is not regularly used as a maintenance treatment because of a shortage, and because an NHS England commissioning policy restricts maintenance use. The EAG excluded maintenance IVIg from its base case. At technical engagement the company updated the proportion of people that have maintenance IVIg in its base case based on data collected as part of the Early Access to Medicines Scheme (EAMS) (see section 3.6; this data is confidential so cannot reported here). A commissioning expert explained that the NHS England commissioning criteria policy for the use of therapeutic immunoglobulin limits the use of maintenance IVIg to rare circumstances. They also provided an estimate of the proportion of people with gMG that have maintenance IVIg (this data is deemed confidential so cannot be reported here), which was substantially lower than the proportion used in the company's base case. The commissioning expert said that the higher proportion of people having maintenance IVIg in the EAMS data may be because people who had efgartigimod through the EAMS were people who urgently needed treatment. At the committee meeting the clinical experts provided estimates of the proportion of people with gMG that would likely have maintenance IVIg, for overall use and by model health state. These were substantially lower than the proportion assumed in the company's base case. The clinical experts said that the proportion of people having maintenance IVIg varies between treatment centres and

IVIg is more frequently used for severe disease. They also explained that maintenance IVIg use can be continuous or intermittent. The committee noted that the company's model included the cost of maintenance IVIg but assumed no clinical benefits. The committee considered that the difference in estimates was likely because different populations were being considered. It recalled it was uncertain which population would have efgartigimod if it was recommended in line with the marketing authorisation (see section 3.3). The committee concluded that the company should estimate the proportion of people having maintenance IVIg in the population in which efgartigimod would be used. If possible, it should use an explicit, valid, and replicable method to estimate the proportion having maintenance IVIg.

Clinical effectiveness

ADAPT and ADAPT+

3.5 The clinical evidence for efgartigimod came from the ADAPT trial and ADAPT extension (ADAPT+) study. ADAPT was a phase 3, multicentre, double-blind, placebo-controlled trial. It recruited adults with a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of 5 points or more with over 50% of the total score attributed to non-ocular symptoms and who were on a stable dose of established clinical treatment. Of the 167 people recruited, 129 (77%) tested positive for AChR antibodies. After the first treatment cycle, 68% of the AChR antibody-positive population who had efgartigimod had a reduction of at least 2 points on the MG-ADL scale (clinically meaningful improvement) compared with 30% of people who had placebo. ADAPT+ is an ongoing, open-label, single-arm, multicentre, 3-year extension of the ADAPT trial. Of the 151 people who rolled over from ADAPT to ADAPT+, 111 (74%) tested positive for AChR antibodies. Data from the January 2022 data cut showed that, on average, a clinically meaningful improvement was achieved in cycles 1 through 14. The committee concluded that efgartigimod as an add-on to established clinical management is more effective at improving MG-ADL score than established clinical management alone.

EAMS and EAMS+

3.6 The EAMS aims to provide people who have a high unmet clinical need with earlier access to promising new unlicensed medicines and medicines used outside of their license. The Medicines and Healthcare Products Regulatory Agency considered that there was unmet need in the AChR antibody-positive population when gMG does not respond to currently available treatments or when these treatments are not suitable. The committee considered that this population had more severe disease than that included in the company's model, with a need for urgent treatment. Efgartigimod was available through the EAMS from May 2022 until its marketing authorisation was granted in March 2023, and since then it has been available through the EAMS+ programme. The company said that the EAMS+ programme will be open until NICE publishes final guidance on efgartigimod. The company explained that it intends to collect additional data through the EAMS to support health technology assessment. The committee noted that the EAMS data was only used to inform the proportion of people who have maintenance IVIg in the company's base case. The committee concluded that the population included in the EAMS and EAMS+ indication was not generalisable to the population outlined in the company's economic model or the population that clinical experts said efgartigimod may be used in.

Economic model

Company's modelling approach

3.7 The company used a state transition model to estimate the cost effectiveness of efgartigimod plus established clinical management compared with established clinical management alone. It included 4 health states based on the MG-ADL total score (MG-ADL below 5, MG-ADL 5 to 7, MG-ADL 8 to 9, and MG-ADL 10 or more) to capture disease severity, as well as crisis and death health states. The clinical experts explained that the MG-ADL health states used in the model should broadly capture differences in costs and quality of life. But, they further

explained that there may be rare circumstances when they do not. They suggested, for example, that someone with the most severe score for a single activity while the other activities are unaffected would have a score of 3 and be included in the least severe health state, but a person could score 1 for all 8 activities and be included in the second-worst health state. gMG exacerbations needing hospitalisation were included in the model as an acute event that could occur in any of the MG-ADL health states and was associated with an additional cost and a utility decrement. The EAG considered that the company's model structure and key assumptions were reasonable. The committee concluded that the company's model structure was appropriate for decision making.

Treatment effect after stopping efgartigimod

3.8 The EAG noted that in the company's original base case, the transition probabilities for people that had permanently discontinued efgartigimod resulted in a notable proportion of people remaining in the MG-ADL below 5 health state after 6 months. The EAG also highlighted that the company had stated in its clarification response that it was not aware of any evidence of a residual treatment effect for efgartigimod. The EAG therefore provided updated transition probabilities assuming that 1% of people remain in the MG-ADL below 5 health state after stopping efgartigimod treatment. At technical engagement, the company provided evidence from additional analysis of ADPAT and ADAPT+ data, real world evidence from the US and evidence from efgartigimod in other indications that it believed supported a residual treatment effect for efgartigimod after treatment had stopped. It updated its base case to assume that 15% of people remain in the MG-ADL below 5 health state after stopping treatment with efgartigimod. The EAG considered that the company's assumption was reasonable and updated its base case to match the company's. The committee noted that this assumption had a substantial effect on the cost-effectiveness results. It concluded that a residual treatment effect after treatment stops was plausible but uncertain. The

committee would have preferred more evidence about the possible residual treatment effect, which should include clinical expert input.

Utility values

Source of utility values

3.9 Health-related quality of life data was collected in ADAPT using the EQ-5D-5L and was mapped to the EQ-5D-3L. The company estimated the utility values for the MG-ADL health states using a regression model that contained a treatment effect coefficient. The company explained that the treatment effect coefficient was statistically significant. It therefore included a treatment effect in the MG-ADL health states in the efgartigimod arm, using utility values 0.105 higher than in the established clinical management arm. The company stated that MG-ADL does not fully capture the effect of efgartigimod, so the benefit of efgartigimod would be underestimated if it were only captured in the model using the transition probabilities. The EAG considered that the method the company used to derive utility values and that including a treatment effect were reasonable. It explained that clinical advice it had received suggested some of the difference in utility values between the 2 arms may be because of differences in corticosteroid use. The committee noted the magnitude of the treatment effect and that it was greater than the utility benefit associated with transitioning to the next less severe MG-ADL health state. The committee further noted that the treatment effect was applied in the MG-ADL below 5 health state, in which the model assumed people would not have efgartigimod, which did not appear valid. The committee noted it had not seen evidence to support the assumption of a treatment effect explained by differences in corticosteroid use between arms. It considered that corticosteroid use in specific MG-ADL health states might not differ substantially between the 2 arms, and noted that people in the MG-ADL below 5 health state were assumed not to use corticosteroids in the model. It highlighted that in the more severe MG-ADL health states, corticosteroid use would be optimised regardless of

whether efgartigimod was used or not. The committee concluded that the same utility values should be used for the 2 arms.

Carer disutilities

3.10 The company said that the symptoms people with gMG experience and their need for support has a substantial impact on carers. Carers' health-related quality of life was not measured in ADAPT and the company did not identify any studies that reported carer disutility in gMG. Instead, the company used a published study that reported carer disutility at different severity stages of multiple sclerosis, measured using the Patient-Determined Disease Steps (PDDS) scale, to map to the MG-ADL and crisis health states. The company said that multiple sclerosis data was chosen because multiple sclerosis and gMG are both chronic, autoimmune conditions with similar symptoms that mainly affect young women. The EAG acknowledged that there are some similarities between multiple sclerosis and gMG. But, it noted that the conditions each have different characteristics that could have an impact on carer health-related quality of life, such as the impact on a person's mobility, which limit the generalisability of the 2 conditions. At technical engagement, the company provided the results of a survey it did exploring the impact of gMG on carers. It said that the survey showed that caregiver responsibilities constitute a large burden on carers. The EAG noted that the survey results should be considered with caution. It explained that the survey was descriptive and did not provide values that could be used directly in the model. The EAG further explained that the population who completed the survey may not be generalisable to the overall population of people with gMG in England. The EAG's base case did not include carer disutilities because it considered that the company had not provided robust evidence for their inclusion. The EAG also received clinical expert advice that most people with gMG are independent and would not need lots of caregiver time. The patient experts explained how gMG has a notable impact on carers and how carers often spend a substantial amount of time providing care. The patient experts noted that carers will sometimes need to help

prevent choking and that this can have a substantial impact on their mental health and prevent carers going out and leading independent lives. The committee recognised that, depending on the severity of the condition, gMG can have a substantial impact on carers' lives.. But it further noted that MG-ADL examines a range of symptoms, while the PDDS focuses on a person's ability to walk, so the committee considered that mapping between MG-ADL and PDDS was not appropriate. The committee noted that carer disutilities contributed substantially to the overall quality-adjusted life year (QALY) gain associated with efgartigimod in the company's model. The committee considered that the disutilities used appeared large and that it had not seen evidence to suggest that a person with gMG and their carer would experience a similar level of disutility. The committee concluded that depending on the severity of the condition, gMG could have a substantial impact on carers' lives, which it would take into account qualitatively. But that the disutilities used in the company's model were not appropriate for decision making without further evidence.

Costs

Corticosteroid complications

3.11 The company said that the published literature shows that higher doses of corticosteroids are associated with higher costs from treating complications. The company identified 3 studies that estimated the costs for corticosteroid-related chronic complications with low- and high-dose corticosteroid use. The company's base case used corticosteroid complication costs from a study in people with systemic lupus erythematosus (SLE) done in Sweden (Bexelius et al. 2013). The company explained that it selected this study because SLE and gMG are both autoimmune conditions. It said that it could also be assumed that costs were comparable between the UK and Sweden because the 2 countries have similar socioeconomic conditions. The EAG used corticosteroid complication costs from a study identified by the company in people with asthma done in the UK (Voorham et al. 2019) and believed

that this study was more representative of costs in the UK. The clinical experts explained that the costs from the Voorham et al. study are unlikely to be generalisable to gMG because asthma does not share similar characteristics. The committee noted that the third study identified by the company (Janson et al. 2018) shared similarities with the other 2 studies as it was done in Sweden and included people with asthma. The clinical experts further explained that in all 3 studies, the doses of corticosteroids and the threshold used in the company's model to define high-dose corticosteroids were notably lower than what they would expect for people with gMG. The clinical experts noted that higher doses of corticosteroids could result in different complications and therefore costs. The committee considered that the Voorham et.al. study excluded key weight-related adverse events such as sleep apnoea. The committee noted that the company had not provided evidence that resource use and costs from Sweden are generalisable to the NHS. It further noted that costs from the Bexelius et al. study were notably higher than the costs from the other studies. The committee was unsure whether SLE is directly generalisable to gMG. It felt that the costs from Bexelius et al. lacked face validity and may be confounded, as the study did not account for condition severity or exclude condition-related costs. The committee concluded that none of the studies identified by the company were suitable for decision making, and that corticosteroid complication costs should be generalisable to NHS clinical practice, applicable to gMG and valued using prices relevant to the NHS.

Cost-effectiveness estimates

3.12 Because of confidential commercial arrangements for efgartigimod and some of the established clinical management treatments, the exact cost-effectiveness results are confidential and cannot be reported here. Only the company's base case incremental cost-effectiveness ratio (ICER) was within the range normally considered to be a cost-effective use of NHS resources. The EAG's base case ICER was substantially above this range.

The EAG's preferred assumptions included:

- not including costs for maintenance IVIg (see section 3.4)
- 15% of people remaining in the MG-ADL below 5 health state 6 months after permanently stopping efgartigimod (see section 3.8)
- using different utility values for the efgartigimod and established clinical management arms (see section 3.9)
- not including carer disutilities (see section 3.10)
- using costs from Voorham et al. to model corticosteroid complication costs (see section 3.11).

The committee considered that the ICERs presented by the company and EAG were uncertain. But it considered that, given the impact of its preferred assumptions, it was highly likely that its preferred ICER would be above the range normally considered a cost-effective use of NHS resources.

The committees' preferred assumptions included:

- using the same utility values for the efgartigimod and established clinical management arms (see section 3.9)
- not including carer disutilities (see section 3.10).

There was uncertainty about the population that would have efgartigimod in the NHS if it was recommended in line with the marketing authorisation. The population considered would likely impact the proportion of people expected to have maintenance IVIg. So the committee considered that none of the IVIg maintenance use scenarios considered by the company and EAG were suitable for decision making (see section 3.4). It also considered that both the company's and EAG's corticosteroid complication analyses were not suitable for decision making (see section 3.11). The committee explained that it would prefer to see an analysis that addresses these issues and included:

- clearly identifying and defining the characteristics of the population who would have efgartigimod (see section 3.3)
- estimating the proportion of people having maintenance IVIg in the population who would have efgartigimod (see section 3.4)
- identifying more evidence about the possible residual treatment effect when treatment with efgartigimod is stopped, which should include clinical expert input (see section 3.8)
- using corticosteroid complication costs that are:
  - generalisable to NHS clinical practice
  - applicable to gMG, and
  - valued using prices relevant to the NHS (see section 3.11).

Other factors

Equality

3.13 The committee noted the patient experts' comments that a person's socioeconomic status and how close they live to a gMG specialist centre may impact their ability to access efgartigimod. The committee also noted the clinical experts' comment that pregnant people may not be able to have efgartigimod until additional information is available. But, the committee noted that access to specialist centres is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation. The committee considered that if efgartigimod was recommended, the decision to use efgartigimod during pregnancy should be made by a patient and their clinician if the clinical benefit outweighs the risks. No other potential equalities issues were identified.

Innovation

3.14 The company and clinical experts considered efgartigimod to be innovative, stating that it had a novel mechanism of action that specifically targets the underlying cause of gMG. The clinical experts also noted that efgartigimod can be given at home, and works rapidly. The committee

considered that all additional benefits of efgartigimod had already been taken into account.

Conclusion

3.15 The committee agreed that further information was needed to address the uncertainties. It considered that the cost-effectiveness estimates presented by the company and EAG were highly uncertain, and that given the uncertainty, it would like to see additional analysis. But the committee considered that, given its preferred assumptions, and based on the analysis it had seen, the cost-effectiveness estimates were highly likely to be above the range that NICE normally considers a cost-effective use of NHS resources. The committee concluded that efgartigimod could not be recommended for treating gMG in adults who test positive for AChR antibodies.

4 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

Megan John

Chair, technology appraisal committee D

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.

Ross Wilkinson
Technical lead

Alan Moore
Technical adviser

Celia Mayers
Project manager(s)

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