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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using efgartigimod in the NHS in England.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: 31 January 2024
- Third evaluation committee meeting: 9 May 2024
- 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 because the company have proposed a target population with more severe disease.

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 substantially 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 solution for infusion vial and £15,307.47 per 1,000-mg solution for injection 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 take 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 and their carers 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 immunosuppressant, 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.

Treatment 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 standard treatment. 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 treatment has started. The committee also noted that the company used efficacy data from the ADAPT trial in its model (see section 3.7). 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 is needed from clinical experts to help define a population in which efgartigimod is both clinically and cost effective. It considered that the characteristics of this population should be clearly defined to enable efgartigimod’s use in the NHS.

**Target population**

3.4 As part of its response to draft guidance consultation, the company held a Delphi panel involving 6 experts from neuromuscular specialist centres to identify a target population description. The company explained that the description it proposed closely aligned with the Early Access to Medicines Scheme (EAMS) eligibility criteria (see section 3.8). It proposed that the target population should be people:

- with active, refractory disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 5 or more (over 50% of MG-ADL score from non-ocular symptoms) and
- who cannot tolerate or are ineligible for standard treatment, or in whom standard treatment has failed. (Standard treatment was defined as a maximal dose of steroids, and at least 2 additional treatments, such as non-steroidal immunosuppressants and rituximab, for an adequate period of time, at an adequate dose.)

The company stated that this population has few alternative treatment options and high unmet need, and could be identified in specialist centres. The EAG noted that the company’s target population description referred to a group of people ineligible for standard treatment. It considered that this group falls outside the licensed indication for efgartigimod, which
states its use as an add-on to standard treatment. The company said that ‘ineligible’ did not refer to all standard treatments, and said it is possible that one of the standard treatments may not be suitable. The EAG considered that the company’s proposed description could be clearer. It proposed an alternative description for the target population which states that people are ineligible for ‘at least one’ of the standard treatments. The committee considered that the company and EAG target population descriptions described notably different populations, with the EAG’s proposed wording potentially including a population with less-severe disease. The committee understood the difficulties of identifying a target population description for a condition with no single universally accepted treatment pathway. The committee concluded that the company’s target population description broadly described the most suitable population to have add-on treatment with efgartigimod, and acknowledged the high unmet need in this population, but some uncertainty remained.

**Maintenance IVIg**

3.5 The company considered that maintenance IVIg is part of established clinical management in the NHS and that it is used 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 substantially restricts maintenance use (see section 3.2). 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 EAMS for efgartigimod (see section 3.8; this data is confidential so cannot be reported here). At technical engagement, a commissioning expert provided an estimate of the proportion of people with gMG that have maintenance IVIg (this data is 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 first evaluation 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, noting higher use in specialist centres, and highlighted that 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 this was implausible. It noted that this biases the cost-effectiveness results in favour of efgartigimod because the company model assumed substantially more IVIg use in the established clinical management arm. The committee considered that the difference in IVIg use 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).

**Maintenance IVIg in target population**

3.6 In response to draft guidance consultation, the company used a Delphi panel to directly estimate the proportion of people eligible for maintenance IVIg in its new target population (see section 3.4). The company updated its base case and assumed maintenance IVIg use of 69.17%, distributed between the MG-ADL 5 to 7, 8 to 9, and 10 or above health states based on clinical expert opinion and weighted by the baseline cohort distribution in the model. The EAG considered the evidence from the Delphi panel was appropriate for the proposed target population, but it noted that the model remained sensitive to maintenance IVIg use assumptions. In response to draft guidance consultation, NICE received a comment from a clinical expert stating there is regional variation but maintenance IVIg is a relatively uncommon treatment. The committee noted that the panellists
recruited to the company’s Delphi panel were all from specialist centres. It noted the panellists were asked to estimate the proportion of people who would be eligible for IVIg, but that this was different to asking about the proportion of people who would actually have maintenance IVIg. It further noted that the panellists were asked to assume there were no issues around the supply of IVIg and were not asked about IVIg use by MG-ADL health state. The clinical experts explained that not everyone who was eligible for maintenance IVIg would have it. A patient expert noted that although they might be considered eligible for maintenance IVIg they have not had it. Another patient expert noted that they would not be able to access maintenance IVIg at their current treatment centre. The committee further noted that the company’s approach to modelling IVIg use did not account for a proportion of people whose disease did not respond to IVIg. Another important limitation in the company’s modelling of IVIg was that it did not account for people who would stop IVIg over the lifetime of the model (which is over 50 years in length). The committee considered that IVIg may be stopped because of adverse events, patient choice or a loss of efficacy. Also, few people, if any, would remain on IVIg for such long periods of time as implied by the modelling. The committee also noted that the company’s model assumed the maximum dosing frequency for IVIg, which may also overestimate IVIg use. The clinical experts noted that IVIg would usually be a last-line treatment and some people may therefore continue it for some time, but they could not advise on how long IVIg might be used. The committee noted that in the company’s base case, undiscounted IVIg acquisition and administration costs accounted for well over £1 million in the established clinical management arm. The committee also noted that there was uncertainty around using MG-ADL scores to estimate IVIg use. This was because other clinical details, alongside MG-ADL score, would likely be used in the NHS when deciding whether to offer IVIg. Overall, the committee concluded that the evidence from the Delphi panel and the company’s approach to modelling IVIg use substantially overestimated the use of maintenance IVIg. It noted that the IVIg estimates and modelling used by the company also impacted other
issues, such as placebo effect (see section 3.12) and treatment effect after discontinuation (see section 3.11). This causes them to have greater impact on cost-effectiveness results. It considered that the model should be updated to model IVIg use in a more appropriate and plausible manner (see section 3.23). It also concluded that because of how IVIg use was estimated and modelled, it could not have confidence in any estimate of IVIg use provided by the company’s model.

Clinical effectiveness

ADAPT and ADAPT+

3.7 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 an 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+

3.8 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. At the first meeting, 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.

Data sources and generalisability

3.9 In response to draft guidance consultation, the company updated the target population description (see section 3.4). The company said that evidence from ADAPT showed that the efficacy observed in the AChR antibody-positive population is generalisable to the updated target population. So, it did not make any changes to the modelling of clinical effectiveness. The EAG stated that there were low levels of certainty around the evidence supporting the generalisability of the clinical-effectiveness estimates. The EAG also considered that age and gender distribution of people enrolled in EAMS should be used in the model. It noted that the company’s proposed target population aligned closely with the EAMS cohort. That cohort was larger than the UK cohort in the MyRealWorld MG study used by the company to inform the baseline age and gender distribution in its revised base case. The company stated that the baseline characteristics of the UK cohort in MyRealWorld MG were similar to those of the EAMS cohort. Therefore, it did not update its base case. The committee noted that no alternative approaches to the modelling of clinical effectiveness were presented to overcome the
uncertainty. The committee concluded that using clinical-effectiveness results from a population broader than the updated target population was a source of uncertainty. The committee considered that baseline characteristics used in the model should align with other inputs, such as quality of life (see section 3.13) and clinical-effectiveness estimates. It therefore concluded that age and gender distribution captured in ADAPT should be used in the model.

Economic model

Company's modelling approach

3.10 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. They would therefore be included in the least severe health state. But, a person who scores 1 for all 8 activities would be included in the second-worst health state. The clinical experts also noted that MG-ADL score would not be used on its own to decide whether IVIg should be offered. 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 that 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 recalled that in the company’s model people did not have a subsequent cycle of treatment with efgartigimod if they remained in the MG-ADL below 5 health state. The clinical experts explained that in clinical practice they would not offer
efgartigimod to people with an MG-ADL score below 5 and would stop treatment if a person’s MG-ADL score falls below 5. The committee concluded that the company’s model structure was generally appropriate for decision making. But, there was some uncertainty with how closely MG-ADL scores inform disease severity, and significant limitations to some aspects of the modelling (see sections 3.6, 3.9, 3.11 and 3.12).

**Treatment effect after stopping efgartigimod permanently**

### 3.11

The EAG highlighted that in the company’s original base case, the transition probabilities for people who 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. So the EAG provided updated transition probabilities assuming that 1% of people remain in the MG-ADL below 5 health state after stopping efgartigimod permanently. At technical engagement, the company provided an additional analysis of ADAPT and ADAPT+ data, real-world evidence from the US and evidence on efgartigimod in other indications that it believed supported a residual treatment effect for efgartigimod after treatment had stopped permanently. 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 and accounted for around 50% of incremental quality-adjusted life year (QALY) gains for efgartigimod in the EAG’s base case. At the first meeting, it concluded that a residual treatment effect after treatment stops was plausible but uncertain. The committee stated it would have preferred more evidence about the possible residual treatment effect, which should include clinical expert input. At the second meeting the company maintained its base-case position, assuming that 15% of people remain in the MG-ADL below
5 health state after permanently stopping treatment with efgartigimod. It provided a statement from one clinical expert who, after reviewing the additional evidence provided at technical engagement, believed a 15% residual effect is plausible. One of the clinical experts at the meeting stated that they could not comment on the plausibility of such an effect. The EAG noted that the population in ADAPT and ADAPT+ was broader than the company’s proposed target population (see section 3.4). It explained that it was uncertain if the company’s proposed target population and the ADAPT populations would have a similar proportion of people with a residual treatment effect after stopping efgartigimod. In response to draft guidance consultation, NICE received a comment from a clinical expert that stated that they were unaware of evidence that some people can stop efgartigimod without a relapse. They further stated that most people seem to need 7- to 8-week cycles and become rapidly symptomatic once treatment is stopped or postponed. The committee considered that the company’s approach to modelling a residual treatment effect after treatment stops continued to be plausible but highly uncertain. The committee noted that the available evidence was limited with short follow up. It further noted that it had not been presented with the reasons for discontinuation in those who maintained an MG-ADL score of below 5 after permanently stopping efgartigimod. The committee recalled that varying the percentage (from 15% to 1%) of people that remain in the MG-ADL below 5 health state after permanently stopping efgartigimod had a substantial effect on the cost-effectiveness results. The committee also noted that treatment effect after permanent discontinuation may be linked to the placebo effect (see section 3.12). But, the committee noted the EAG’s comments that the company’s model could not adjust the treatment effect after permanent discontinuation assumptions, while also retaining the placebo effect in the established clinical management arm. The committee considered that it would like to see further input on this issue (see section 3.23). It concluded that it would consider the company’s assumption alongside other scenarios, but noted the uncertainty associated with these assumptions.
Placebo effect

3.12 In the company’s model, the transition probabilities for the first 4 model cycles in the established clinical management arm were derived from observations over the first 16 weeks in the placebo arm of ADAPT. After the fifth model cycle, people in the established clinical management arm were assumed to return to baseline health state distribution and remain in the same health state unless a crisis or death occurred. The company stated that this assumption was conservative because it meant that the condition would not get worse. After the first meeting, the NICE technical team asked the company to explain:

- why the observed effect in the established clinical management arm would not persist over the long term and
- if it believed the observed effect was due to any of the following mechanisms:
  - regression to the mean (a tendency for extreme values to move closer to the mean when measures are repeated over time)
  - a trial effect (benefit from being in the trial that would apply to both arms, and not in routine practice)
  - a ‘true placebo’ effect (benefit from the expectation that treatment may lead to improvement, which would apply to both arms, and may apply in practice).

The company noted that the average duration of established clinical management from disease diagnosis was 9.3 years in the AChR antibody-positive population in ADAPT. It also noted that the ADAPT inclusion criteria required people to have an MG-ADL score of at least 5, despite treatment with established clinical management. The company stated that this suggested that established clinical management would be unlikely to reduce disease activity. The company explained that no long-term data from the placebo arm of ADAPT is available. The company believed that regression to the mean, a trial effect and a placebo effect all likely played a role in the observed response. But, it stated that these mechanisms are
specific to a trial setting. The company recalled that in ADAPT, 30% of the established clinical management arm had an MG-ADL response. It suggested that a response of this size could likely only be attributed to a placebo effect. The company stated that in its model the efgartigimod cohort are assumed to worsen during the off-treatment period after each treatment cycle and after permanent treatment discontinuation. The EAG considered the company’s approach to modelling the established clinical management arm was reasonable. The committee noted that randomised controlled trials, such as ADAPT, provide evidence for relative treatment effects. It considered that by assuming that the observed effect in the established clinical management arm does not persist, the company’s model no longer reflected the relative treatment effect observed in ADAPT and instead artificially inflated the treatment effect. This problem was compounded when assuming a treatment effect for efgartigimod persists after permanently stopping treatment (see section 3.11). The committee noted the size of the response observed in the placebo arm. But, it believed that it was unlikely that a true placebo effect would have such a response and instead it was most likely a statistical consequence of regression to the mean. The committee agreed that in the model the efgartigimod cohort should be assumed to worsen during the off-treatment period. But it did not consider that this justified removing the observed treatment effect from the established clinical management arm. The committee therefore concluded that the benefit observed in the placebo arm of ADAPT should be maintained over the time-horizon of the model.

Utility values

Source of utility values

3.13 Health-related quality of life data was collected in ADAPT using the EQ-5D-5L and was mapped to the EQ-5D-3L. At the first meeting, the company’s model used utility values 0.105 higher in the efgartigimod arm 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 using higher utility values in the efgartigimod arm 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 difference in utility values between the 2 arms 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 company’s model used higher utility values in the efgartigimod arm for 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 higher utility values used in the efgartigimod arm for example, due to 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 in the model it was assumed people in the MG-ADL below 5 health state would not use corticosteroids. 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. In response to draft guidance consultation, the company revised its base case to use the same utility values from the MyRealWorld MG study for the 2 arms. It considered that data from MyRealWorld MG (a prospective, observational, longitudinal study that aimed to capture the impact of MG from the perspective of people with the condition) was more accurate than data collected in ADAPT. The company proposed that because data from ADAPT was collected in a clinical trial setting, where people were monitored closely, this may have resulted in overvaluation of health state utility. It considered that using pooled data from ADAPT would include some of the effect of efgartigimod. It highlighted that data from MyRealWorld MG is representative of people having established clinical management, including immunoglobulins and rituximab. The EAG noted that the
populations included in both ADAPT and MyRealWorld MG are different to the new proposed target population (see section 3.4). It further stated that it considered the MyRealWorld MG study to be at high risk of bias. The EAG considered that there remained significant uncertainty around the source of health state utility values, but that utilities from the EAMS or the subgroup in ADAPT that meets the new target population description would be more appropriate. The committee noted that the NICE health technology evaluations manual states that EQ-5D data can be sourced from the literature when it is not available in the relevant clinical trials. It recalled that EQ-5D data was available from ADAPT. The committee considered that utility values used in the model should align with other inputs, such as the baseline characteristics (see section 3.9) and clinical-effectiveness estimates. On balance, the committee concluded that pooled utility values from ADAPT should be used in decision making.

**Carer quality of life**

3.14 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. Instead, in its original base case, 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 conducted 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 interpreted 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 QALY gain associated with efgartigimod in the company’s model. The committee considered that the carer 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.

**Updated carer disutilities**

3.15 In response to draft guidance consultation, the company updated its base case to include disutilities obtained from 2 unpublished studies. The company noted that in these studies the utility values of the carers
generally declined with the severity of the condition but that no linear relationship was found. The EAG explained that the lack of linear relationship could result from the small sample size. It further explained that these studies did not include a matched-control group so it could not determine if the utility decrements were only from caregiving. The EAG noted that the 2 studies were observational and potentially subject to selection bias because people taking part were self-selecting. In response to draft guidance consultation, NICE received a comment from the ABN stating that comparison of carer support is not appropriate in an MG population. The committee considered that because the disutilities presented at the second meeting were collected from carers of people with gMG they were potentially more appropriate and relevant than the disutilities presented at the first meeting. The committee recognised that the availability of carer disutilities data sources are often limited. But, it noted the limitations identified by the EAG and that some of the values lacked face validity. The committee concluded that it would continue to take into account the impact on carers’ lives qualitatively in its preferred assumptions for decision making.

Costs

Corticosteroid complications

3.16 The company said that the published literature shows that higher doses of corticosteroids are associated with higher costs from treating complications. In its original submission, 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 the second study identified by
the company, which was in people with asthma in the UK (Voorham et al. 2019). The EAG 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 because 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, because 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. It also concluded that corticosteroid complication costs should be generalisable to NHS clinical practice, applicable to gMG and valued using prices relevant to the NHS.

**Updated corticosteroid complication costs**

3.17 In response to draft guidance consultation, the company updated its base case to use corticosteroid complication costs derived from NHS reference costs and the frequency of corticosteroid-related adverse events from a US study in people with MG (Lee et al. 2018). The company’s updated base case applied the same costs for both low- and high-dose corticosteroid use. The EAG considered that the company’s estimates of
complication costs were not fit for purpose and lacked face and methodological validity. It explained that it had concerns related to the use of adverse event frequencies reported by Lee et al. and the approach taken by the company to assign costs. The EAG provided a scenario in which corticosteroid complication costs were applied only for people in Lee et al. who found their side effects intolerable. In response to draft guidance consultation, NICE received a comment from a clinical expert who suggested that most people with refractory disease will have stopped taking steroids because they were not effective. The committee recognised that the corticosteroid complication costs used in the company’s revised base case used data from a study in people with MG. But, it felt that the costs lacked face validity. The committee considered that some of the costs used were not appropriate and that some of the complications considered would be treated as part of ongoing routine care. The committee recalled the clinical expert comment received during draft guidance consultation. It considered that it was likely that some of the people captured in the company’s proposed target population description would have stopped having corticosteroids. The committee concluded that the EAG’s scenario, in which costs were only applied for people in Lee et al. who found their side effects intolerable, was appropriate for decision making.

**Subcutaneous formulation of efgartigimod**

3.18 In response to draft guidance consultation, the company stated that both subcutaneous and intravenous formulations of efgartigimod will soon be licensed. The company provided a scenario analysis that assumed 80% of people had the subcutaneous formulation while 20% had the intravenous formulation. Acquisition and administration costs were adjusted accordingly but it was assumed all other costs and outcomes were unchanged. The company stated that the subcutaneous formulation would enable faster administration, reducing burden on people with gMG, carers and healthcare providers. The clinical experts explained that it is difficult to estimate the exact proportion of people who would have the
subcutaneous formulation, but that 80% was a reasonable assumption because of the potential additional benefits. The committee concluded that a scenario in which 80% of people have the subcutaneous formulation was appropriate for decision making. But, the committee recognised that it would not be able to recommend efgartigimod based on these assumptions until the subcutaneous formulation is included in the marketing authorisation.

Cost-effectiveness estimates

3.19 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.

3.20 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 substantially above the range usually considered a cost-effective use of NHS resources.

The committee’s preferred assumptions

3.21 The committee’s preferred assumptions included:

- using population characteristics from ADAPT (see section 3.9)
- considering a range (1% to 15%) of people remaining in the MG-ADL below 5 health state 6 months after permanently stopping efgartigimod (see section 3.11)
- maintaining the benefit observed in the placebo arm of ADAPT over the time-horizon of the model (see section 3.12)
• using the same pooled utility values from ADAPT for both the efgartigimod and established clinical management arms (see section 3.13)
• considering carer disutilities qualitatively (see section 3.15)
• including corticosteroid complication costs only for people in the Lee et al. study who found their side effects intolerable (see section 3.17)
• 80% of people having the subcutaneous formulation and 20% having the intravenous formulation (see section 3.18).

The committee considered that the company’s target population (see section 3.4) broadly described the most suitable population to have add-on treatment with efgartigimod but there was still some uncertainty. The ADAPT and ADAPT+ studies recruited a broader population than the one covered by the company’s target population description. So, using data from these studies to inform modelling assumptions was also associated with uncertainty (see section 3.9). The committee noted that the cost-effectiveness estimates were highly sensitive to changes in maintenance IVIg use. It considered that the evidence from the Delphi panel and the company’s approach to modelling IVIg use substantially overestimated the use of maintenance IVIg. It could therefore have no confidence in these estimates.

Acceptable ICER

3.22 NICE’s health technology evaluations manual notes that, above a most plausible ICER of £20,000 per QALY gained, decisions about the acceptability of the technology as an effective use of NHS resources will consider the degree of uncertainty around the ICER and any benefits of the technology that were not captured in the QALY calculations. The committee will be more cautious about recommending a technology if it is less certain about the evidence presented. The committee noted the high unmet need in the company’s target population (see section 3.4). The committee also noted that gMG could have a substantial impact on carers’ lives (see section 3.15). The committee agreed that the maximum
acceptable ICER would be at the upper end of the £20,000 to £30,000 per QALY gained range that NICE considers a cost-effective use of NHS resources. But, this would require the areas of outstanding uncertainty to be resolved (see section 3.21).

Additional analysis

3.23 The committee outlined the analysis that it would like to see the company provide. In particular, it stated that IVIg use should be modelled to address the wide range of committee concerns (see sections 3.5 and 3.6). These concerns included:

- the IVIg use assumed for MG-ADL health states was likely overestimated because the question in the company’s Delphi panel asked about eligibility rather than uptake and assumed no supply issues
- there was no discontinuation modelled for IVIg but it may be stopped, for example, because of adverse events, lack of clinically meaningful response or patient choice
- no QALY benefit was assumed for IVIg use, which biased cost-effectiveness results in favour of the efgartigimod arm
- maximum dose frequency was assumed.

The committee would also like to see further analysis and input on:

- Treatment effect after permanent discontinuation (see section 3.11), including specific input on:
  - the plausibility of a residual treatment effect once efgartigimod has been stopped permanently and how this is biologically possible
  - how long a residual treatment effect may persist if an effect is plausible
how the effect may be linked to the placebo effect (see section 3.12)

- The generalisability of data used in the model to estimate the cost-effectiveness of efgartigimod in the company’s target population (see sections 3.4, 3.7 to 3.9), including:
  - Further input on how baseline characteristics, treatment effectiveness, utility values, and other model inputs compare to what would be expected in a population with a more severe disease (as proposed by the company).

Other factors

Equality

3.24 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

3.25 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

3.26 The committee 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 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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