NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Zilucoplan for treating antibody-positive generalised myasthenia gravis

1 Recommendations

1.1 Zilucoplan 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 zilucoplan 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

Standard treatment for generalised myasthenia gravis in adults who test positive for anti-acetylcholine receptor antibodies includes surgery to remove the thymus gland, acetylcholinesterase inhibitors, corticosteroids and non-steroidal immunosuppressant treatments (NSISTs). For people whose condition does not improve with standard treatment, intravenous immunoglobulin or plasma exchange may also be used. Zilucoplan would be used as an add-on to standard treatment, for people who test positive for anti-acetylcholine receptor antibodies and whose condition has not improved with standard treatment alone.

Clinical trial evidence suggests that zilucoplan plus corticosteroids and NSISTs improves symptoms and people's ability to carry out their normal activities compared

Issue date: June 2025

with standard treatment alone. But there are uncertainties in zilucoplan's treatment effect compared with intravenous immunoglobulin and plasma exchange.

There are also substantial uncertainties in the economic model. Although the economic model suggests some benefits with zilucoplan, this is at a substantial additional cost because zilucoplan is an add-on to standard treatment. The most likely cost-effectiveness estimates are substantially above the range NICE considers an acceptable use of NHS resources. So, zilucoplan is not recommended.

2 Information about zilucoplan

Marketing authorisation indication

2.1 Zilucoplan (Zilbrysq, UCB Pharma) is indicated 'as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients 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 zilucoplan.

Price

2.3 The list price of zilucoplan is £3,653.97 for 7 pre-filled syringes of 16.6 mg solution for injection, £5,041.78 for 7 pre-filled syringes of 23.0 mg solution for injection, and £7,114.70 for 7 pre-filled syringes of 32.4 mg solution for injection (all excluding VAT, BNF online, accessed June 2024).

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

3 Committee discussion

The evaluation committee considered evidence submitted by UCB Pharma, 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 (anti-AChR) antibodies. The patient experts explained the condition can have substantial physical, emotional and financial impacts on the person with gMG, as well as their family. They noted that the typical symptoms of fatigue, and problems with breathing, speaking, seeing and concentrating, substantially impact daily activities and ability to work. The symptoms of gMG mean that many people regularly need a high level of care. All current treatments for gMG aim to suppress the condition to reduce symptoms and there is no cure. The patient experts noted that treatments for gMG are associated with side effects, and it is particularly difficult to manage the side effects of multiple treatments simultaneously. Many people with gMG take corticosteroids, but it can be difficult to optimise the lowest effective dose (to minimise side effects) without increasing the risk of exacerbations (an acute worsening of symptoms) or myasthenic crisis. People with gMG and their carers spend their lives fearing a myasthenic crisis, a life-threatening complication of gMG in which the muscles that control breathing are affected, and hospitalisation is required. The patient experts explained that there are limited options available for people whose condition does not improve with standard treatment (refractory gMG). Typically, people with refractory gMG will have intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), or try a different type of immunosuppressant. IVIg and PLEX both require regular hospital visits

or stays. These can be difficult to fit around work and family commitments, and place substantial burden on carers. The patient experts highlighted the unmet need for treatments for refractory gMG. The committee concluded that gMG is a debilitating condition with a high treatment burden.

Clinical management

Treatment options

3.2 gMG is a long-term 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, at the time of this evaluation, the ABN guidelines are being updated. The ABN (2015) guidelines recommend that people are first offered pyridostigmine (an acetylcholinesterase inhibitor) at the lowest effective dose and that surgery to remove the thymus gland (thymectomy) can be considered for people under 45 years. The clinical experts noted that, after publication of the ABN guidelines, thymectomy is now offered to people under 65 years. If symptoms continue, people are offered prednisolone. The clinical experts explained that corticosteroids like prednisolone have side effects and that they aim to use minimal effective doses to reduce these. The ABN guidelines recommend non-steroidal immunosuppressant treatments (NSISTs) such as azathioprine if remission is not achieved on corticosteroids alone. If there is an insufficient response to immunosuppressants or people experience notable side effects on increasing corticosteroid doses, expert advice should be sought on using IVIg or PLEX. The NHS England commissioning criteria policy for the use of therapeutic immunoglobulin recommends IVIg should be used:

- when urgent inpatient treatment is needed and PLEX 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.

Rescue treatments for a myasthenic exacerbation or crisis include IVIg or PLEX. The clinical experts explained that zilucoplan would be used as an alternative to long-term maintenance IVIg or PLEX, but would not replace rescue use. They highlighted that IVIg and PLEX are time-consuming and resource-intensive treatments, and that access to PLEX is highly variable across the NHS. NHS England stated that rituximab and acetylcholinesterase inhibitor treatment could be considered for refractory gMG. But clinical advice received by the company and EAG suggested that the evidence for rituximab in refractory gMG is limited, and it takes a long time to start working. The clinical experts advised that rituximab is being used earlier in the treatment pathway and is less widely used for refractory gMG. The committee concluded that an effective, fast-acting, and easy-to-administer treatment option would be welcomed by people with gMG and healthcare professionals.

Target population

3.3 Zilucoplan has a marketing authorisation as an add-on to standard treatment for AChR antibody-positive gMG. In its submission, the company positioned zilucoplan for a narrower population, people with refractory AChR antibody-positive gMG, based on the following criteria:

- the condition has not responded to systemic treatments, including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and ciclosporin, or these options are contraindicated or not tolerated, and
- the condition is uncontrolled, defined by a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 6 or more or a Quantitative Myasthenia Gravis (QMG) score of 12 or more, and:
  - an additional treatment such as IVIg or PLEX is being considered, or

  - people are having long-term treatment with IVIg or PLEX, or
  - efgartigimod would be an alternative option (subject to NICE evaluation).

The committee was aware that the criteria for the company's target population were based on the pre-planned refractory subgroup of the RAISE trial (see section 3.6), which included:

- people on treatment for at least 1 year with at least 2 of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, or other immunosuppressant treatments, or
- people on treatment for at least 1 year with at least 1 of these therapies, and who required PLEX, IVIg or subcutaneous immunoglobulin (SCIg) at least every 3 months for the 12 months before enrolment.

During the first committee meeting the EAG stated that the definition for the refractory subgroup in RAISE, which specified that treatment must have been tried and not responded to for 1 year, was slightly narrower than that for the company's target population. But it considered the definition of refractory in RAISE was appropriate. The clinical experts noted that the criteria for the company's target population broadly describes the population that zilucoplan would be used for in the NHS. The clinical experts did not consider it appropriate to set a time limit when defining refractory gMG, because sometimes it is straightforward to identify who has refractory gMG and they would not wait 1 year before trying other treatments. The committee considered that the target population defined in the company submission was similar to the population that would have zilucoplan in the NHS, but the definition of refractory was uncertain.

In response to the second draft guidance consultation, the company

revised the wording of the first criterion for its target population to be more specific, requiring people to have had 2 or more NSISTs, specifically:

- the condition has not responded to adequate treatment with steroids and at least 2 NSISTs, or these options are contraindicated or not tolerated, and
- the condition is uncontrolled, as defined by an MG-ADL score of 6 or more or a QMG score of 12 or more, and
- an additional therapy such as IVIg or PLEX is being considered, or the gMG is being treated chronically with IVIg or PLEX

The EAG considered that, in the absence of established definition of refractory gMG, either wording of the company's target population may be legitimate. But it noted the company's revised wording may be more aligned with the company's interpretation of the efgartigimod Early Access to Medicines Scheme (EAMS) cohort to support its use of a narrower EAMS cohort in the economic model (see section 3.5).

During the third committee meeting, the committee questioned whether the company's revised target population would unnecessarily narrow the population eligible for zilucoplan in clinical practice. The company explained that its target population remains the same, but this change to the wording of its target population was to make it more specific and align with UK clinical practice. The clinical experts explained that, if recommended, zilucoplan would be used only for people with severe refractory gMG, as an add-on treatment for people who are considered for, or on long-term use of IVIg or PLEX. The clinical experts also agreed that the company's revised wording is strict, but fair and workable. The patient expert also agreed that the revised wording is appropriate. Considering the absence of established criteria for refractory gMG in practice and the clinical and patient experts opinions, the committee agreed that the company's revised target population that specifies the condition 'has not responded to adequate treatment with steroids and at

least 2 NSISTs or these options are contraindicated or not tolerated' reflects those who would have zilucoplan in the NHS and was appropriate.

Comparators

3.4 The final scope issued by NICE listed the following comparators:

- standard care without zilucoplan (including corticosteroids and NSISTs, with or without IVIg or PLEX)
- efgartigimod (subject to NICE evaluation)
- ravulizumab (subject to NICE evaluation, now terminated).

The company proposed the following comparators at the first committee meeting: efgartigimod, IVIg and PLEX, excluding corticosteroids and NSISTs. At the time of this evaluation (13 June 2024 [first committee meeting] to 5 Feb 2025 [third committee meeting]), the NICE evaluation of efgartigimod for treating gMG was ongoing and so efgartigimod was not considered as established NHS practice. The committee noted that zilucoplan, IVIg and PLEX are intended to be used as an add-on treatment to corticosteroids and NSISTs. So, corticosteroids and NSISTs should be included in both arms of the model. The clinical experts commented that the access to IVIg and PLEX varies substantially across the NHS. Some centres may exclusively use IVIg, some may use a mix of IVIg and PLEX, and some may have access to neither. So, some people would try another type of NSIST instead of IVIg or PLEX. To reflect this, the EAG preferred to use a 'basket' of standard care as the comparator. In this, some people have IVIg (plus corticosteroids and NSISTs), some have PLEX (plus corticosteroids and NSISTs), and some have corticosteroids and NSISTs only. The EAG assumed that data on the proportion of people having each treatment from the efgartigimod EAMS would be relevant for this evaluation. The EAG noted that, although 'refractory' was defined in a slightly different way, people in the efgartigimod EAMS were largely comparable to the population who would have zilucoplan in the NHS. The EAMS cohort (Dionísio et al. 2024)

included 48 people with refractory gMG in the NHS (average MG-ADL at baseline, 11.2) who previously had 1 or more NSISTs (average, 2.6). At the first committee meeting, the EAG noted that, among these 48 people, at the time of starting efgartigimod:

- 43.8% were having long-term IVIg (plus corticosteroids and NSISTs)
- 14.6% were having long-term PLEX (plus corticosteroids and NSISTs)
- 41.6% were having only corticosteroids and NSISTs.

During the first committee meeting, the committee concluded that a 'basket' of standard care is consistent with the NICE scope, is more reflective of NHS practice and is the relevant comparator. The committee also agreed with the EAG that corticosteroids and NSISTs should be included in both arms, and that the proportion of people having each treatment could be taken from the EAMS population.

Proportion of people on treatments in the basket comparator

3.5 In response to the first draft guidance consultation, the company included the 'basket' of standard care (which it referred to as 'refractory standard care') as the subsequent treatment in its revised economic model that was presented to the second committee meeting (see section 3.15). The company disagreed with the EAG's preference for using the 'basket' of standard care as the comparator. This is because it thought that zilucoplan would displace IVIg and PLEX for people with refractory gMG that has not responded to corticosteroids or NSISTs. It also considered that the overall EAMS cohort (n=48) had less severe gMG than the refractory population from RAISE or those who would have zilucoplan in practice. To address this, the company revised the proportions of people having IVIg, PLEX, and corticosteroids and NSISTs in the economic model. It did this by removing people from the EAMS cohort whose condition was not considered refractory, who had no treatment (who would not be eligible for zilucoplan because it is licensed as an add-on treatment), and who were on corticosteroids only (who would likely try an

NSIST before starting zilucoplan). The company's revised EAMS cohort included a smaller population (n=37) than the overall EAMS cohort (n=48) and comprised:

- 56.7% having long-term IVIg (plus corticosteroids and NSISTs)
- 18.9% having long-term PLEX (plus corticosteroids and NSISTs)
- 24.4% having only corticosteroids and NSISTs.

During the second committee meeting, the company explained that the inclusion criteria for EAMS were designed specifically for efgartigimod, and based on a broader population that included some people whose condition would not be considered refractory in practice. The clinical expert also explained that there are slightly different definitions for refractory gMG in practice. They explained that it was less severe in the EAMS cohort than the RAISE refractory population and those who would have zilucoplan in the NHS. The EAG considered that the company's revised proportions were appropriate. But the EAG noted the company's disagreement with using the 'basket' of standard care (which the company referred to as 'refractory standard care') as the relevant comparator and the company's preference to use this to model the proportions of subsequent treatments that people would have after zilucoplan (see section 3.15 to 3.16). The committee noted that the EAMS for efgartigimod was intended for refractory gMG that had not responded to 2 or more NSISTs or when these treatments were not suitable or not tolerated, and that was being regularly managed with IVIg and PLEX. It also noted that there is variation in how refractory populations have been defined in RAISE and the EAMS cohort, and that there remained considerable uncertainty about which definition of refractory gMG was more appropriate for the company's proposed target population for zilucoplan at the time of the second committee meeting (see section 3.3). The committee was concerned about restricting the refractory target population so that access to zilucoplan would only be possible if people with refractory gMG had exhausted all prior treatment options. It also

remained unclear how refractory gMG was defined for the EAMS or by the company. So the committee requested that the company clarify its target population for zilucoplan, and provide further evidence and rationale to support its preference for a revised EAMS cohort to inform its preferred 'refractory standard care basket'.

During the third committee meeting, the company maintained that IVIg and PLEX were the only relevant comparators, but provided an alternative base case in the economic model comparing zilucoplan with its revised 'refractory standard care basket'. The company explained that the inclusion criteria for the overall EAMS cohort (Dionísio et al. 2024) were aimed at recruiting people with refractory gMG but not all people in the cohort met the inclusion criteria. It considered that 77% (37/48) of people in the EAMS cohort were designated as having refractory gMG, which clinical feedback to the company during the consultation of the second draft guidance agreed was reasonable. It stated that 3 people in EAMS were not having any treatment and 10 people were on corticosteroids only, which meant these 13 people did not have refractory gMG. To match the number of people designated as refractory in the EAMS cohort (n=37), the company included 2 people on corticosteroids only as having refractory gMG to reflect those who might have previously had NSISTs. The EAG commented that the company's rationale for classifying 2 people on corticosteroids only as having refractory gMG was self-contradictory. It also highlighted some uncertainties in the reporting of the EAMS cohort publication (Dionísio et al. 2024). For example, the reporting on number of people on standard care treatment was not mutually exclusive in the publication because more than 1 reason for starting efgartigimod could be selected. The EAG stated that not all people in the EAMS cohort would necessarily meet the criteria for refractory gMG as defined by the EAMS cohort's inclusion criteria, but the reporting of Dionísio et al. (2024) was not clear and the company's revised EAMS cohort reduced the already small population size to just 37 people. The EAG considered that the

overall EAMS cohort (n=48) would more appropriately reflect the heterogeneous population with refractory gMG in clinical practice. The committee did not consider it appropriate to remove people having corticosteroids only from the EAMS cohort study. This is because these people could have had refractory gMG if they had previously stopped other treatments for refractory gMG based on loss of response. One clinical expert at the third committee meeting explained that the company's revised EAMS cohort aligns with its revised wording for the target population of zilucoplan (see section 3.3). However, the committee noted the further reduced sample size of the revised EAMs cohort. It also noted the reporting of the EAMS publication is not clear about how the criteria for being refractory and so eligible for efgartigimod, as set out in its inclusion criteria, were applied across treatment centres during patient recruitment and there may be variations. It considered that a relatively larger sample size of the overall cohort may be more representative of how refractory gMG would be classified in practice, having in mind that there is no standardised criteria or mandatory definition of refractory gMG in clinical practice or guidelines. Recognising there may be variations across centres in identifying refractory gMG, the committee considered that the identification of refractory gMG in the overall EAMS cohort (n=48) may more closely reflect the identification of refractory gMG for treatment with zilucoplan in the NHS. It therefore concluded that that the overall EAMS cohort is appropriate to inform the proportion of people on treatment in the 'basket' of standard care.

Clinical effectiveness

RAISE

3.6 RAISE was a phase 3, randomised, multicentre, double-blind, placebo-controlled trial. It recruited adults with gMG with positive serology for anti-AChR antibodies, with an MG-ADL score of 6 or more and a QMG score of 12 or more. Of the 239 people screened, 174 were randomised to zilucoplan (n=86) or placebo (n=88). People in both arms also continued

to have standard treatment with existing corticosteroids and NSISTs. The primary outcome was reduction in MG-ADL score at 12 weeks. From baseline to week 12, people who had zilucoplan had a significantly greater reduction in MG-ADL score compared with people who had placebo (4.39 versus 2.30, least squares mean difference of -2.09 [standard error: 0.58; 95% confidence interval: -3.24, -0.95; p<0.001]). RAISE also reported the number of people who had an MG-ADL response, defined as a 3-point or more improvement in MG-ADL score, as a secondary outcome. At week 12, significantly more people who had zilucoplan had an MG-ADL response than people who had placebo (73.1% versus 46.1% [odds ratio: 3.18; 95% confidence interval: 1.66, 6.10; p<0.001]). The EAG noted that a high proportion of people who had placebo had an MG-ADL response. The patient and clinical experts explained that people with refractory gMG can feel hopeless because there are no further treatment options. They thought it was plausible that the high level of expectation that a new treatment will work could translate to a perceived improvement in symptoms. The committee noted that gMG can relapse and remit over time. It questioned whether people might enter the trial when their gMG is particularly bad, and the improvement seen after starting treatment is partly a regression to the mean effect. The clinical experts thought this was possible, but highlighted the difference in response observed between the treatment groups as evidence of the benefits of zilucoplan. RAISE also included a pre-planned subgroup of people with refractory gMG. Refractory gMG was defined similarly to the definition of the target population in the company's submission (see section 3.3), with the additional criterion that people had at least 1 year of standard treatment. A total of 88 people (51%) in RAISE had gMG that met the refractory definition. The outcomes of people in the refractory subgroup are considered confidential by the company and so cannot be reported here. The committee concluded that zilucoplan as an add-on to standard treatment is more effective at improving MG-ADL score than standard treatment (corticosteroids and NSISTs) alone. The committee noted the

substantial response in the placebo group and emphasised the need for this to be accounted for in any indirect treatment comparisons.

RAISE-XT

3.7 RAISE-XT is an ongoing open-label extension trial. People could enter RAISE-XT after completing 12 weeks of RAISE, or after completing a zilucoplan phase 2 trial. A total of 200 people entered RAISE-XT. People who had placebo in RAISE could switch to zilucoplan. At the RAISE-XT data cut (May 2023), people who had zilucoplan had a reduced MG-ADL score compared with baseline, and this reduction was maintained through extension week 84 (96 total weeks of treatment). The exact results are considered confidential by the company and so cannot be reported here. The committee concluded that RAISE-XT provided evidence that the effectiveness of zilucoplan was sustained for up to 2 years.

Generalisability

3.8 In its submission, the company positioned zilucoplan for people with refractory gMG (see section 3.3). The EAG noted that people with refractory gMG were only a subgroup of the RAISE trial population. It was concerned that the outcomes observed in the whole RAISE trial population would not generalise to the refractory population that would have zilucoplan in the NHS. It also noted that, of the studies included in the network meta-analysis (NMA; see section 3.9), only RAISE had a pre-planned refractory subgroup, and therefore the assumption of generalisability may not hold for any indirect comparisons. But clinical advice to the EAG explained that the baseline characteristics of the whole RAISE trial population largely approximated the refractory population in the NHS who would be considered for IVIg or PLEX. The clinical experts at the first committee meeting also noted that refractory gMG may be expected to respond as well as non-refractory gMG in trials of new treatments. This is because treatments like zilucoplan have a novel mechanism of action, which people with refractory gMG will not have previously tried and to which their gMG may respond. At the third

committee meeting, the clinical experts also commented that the treatment effect with zilucoplan in the overall trial population of RAISE would be generalisable to the company's revised target population. The committee concluded that the outcomes of the whole trial populations in RAISE and RAISE-XT could be generalised to the refractory gMG population in the NHS.

Indirect treatment comparisons

3.9 There was no head-to-head comparison between zilucoplan and IVIg, and zilucoplan and PLEX. So the company did NMAs comparing the treatment effect of zilucoplan with IVIg and PLEX. For its original NMAs submitted to the first committee meeting, the EAG was concerned that differences in baseline characteristics and placebo response rates across included studies were not adjusted for in the NMAs. It was also concerned that the uncertainty in the NMAs was not carried through into the modelling because the response rate estimates were included as point estimates, without credible intervals. At the first meeting, the committee also noted that several IVIg and PLEX studies were excluded from the NMA because they did not report the MG-ADL response outcome. The committee would have preferred the company to try different methods to obtain estimates of relative differences in those studies so that both IVIg and PLEX could be included in the NMAs. So, it asked the company to provide additional analyses to address these.

Revised indirect treatment comparisons at the second committee meeting

3.10 At the second committee meeting, the company provided 3 sets of updated NMAs to address the committee's and EAG's concerns. These included baseline risk-adjusted NMAs, unanchored MAICs and a bivariate NMA. The EAG noted that baseline risk-adjusted NMAs assessed the probable impact of the differences in placebo response across studies, but these analyses did not include data for IVIg and did not inform the economic model. The company also did 2 unanchored MAICs of

zilucoplan versus IVIg, but the EAG noted that the MAICs did not reduce the uncertainty in the relative effectiveness of zilucoplan because they were not incorporated into the economic model. The company also presented a bivariate NMA for the MG-ADL outcome and used QMG outcomes to estimate MG-ADL when this outcome was missing. One additional study comparing IVIg with placebo was also included in this bivariate NMA. And the results of the bivariate NMA were used to inform the economic model. But the EAG commented that while the statistical approach to the bivariate NMA seemed appropriate, the statistical code had not been provided and so it was unable to verify whether the company had implemented the NMA correctly. The company also used a referent placebo response rate to adjust for differential placebo response across included studies. But the committee noted it would have been preferable to account for differential placebo response within an NMA methodology. The EAG also highlighted that, in addition to the differential placebo response across studies not being accounted for, none of the heterogeneities in baseline population characteristics across studies were adjusted for in the model. And there were no studies on PLEX included in any NMAs and so the relative effectiveness of zilucoplan against PLEX remained highly uncertain. The committee noted that the bivariate NMA provided by the company was an improvement over its original NMA because it allowed the inclusion of an additional study comparing IVIg with placebo. However, it was concerned with the uncertainties highlighted by the EAG and that the uncertainties from the NMAs were not incorporated into the model. So for the second consultation period, the committee requested that the company explore:

- including PLEX in the NMAs by trying to link the networks using IVIg as the common comparator instead of placebo
- adjusting for differential placebo response as well as baseline population characteristics across studies included in the NMAs
- incorporating the uncertainties from the NMAs into the model.

Revised indirect treatment comparisons at the third committee meeting

3.11 In response to the second draft guidance consultation, the company provided 3 sets of NMAs. These were supported by an updated systematic literature review designed to identify further evidence on IVIg and PLEX, for the MG-ADL response and change in MG-ADL from baseline outcomes. The provided NMAs included bivariate NMAs, updated baseline risk-adjusted NMAs, and a new 2-stage NMA. The bivariate NMAs, which informed the company's base case in the model, included 4 additional studies on IVIg and PLEX including Barth et al. (2011). The bivariate NMAs enabled missing MG-ADL outcomes to be predicted from QMG outcomes, maximising the available relevant outcomes and inclusion of PLEX in the comparisons. The baseline risk-adjusted NMAs adjusted for differential placebo response and baseline population heterogeneity across studies included in the NMAs. But the company did not use it to inform the model because no study on PLEX was included in this analysis. The 2-stage NMA comprised a baseline risk-adjusted NMA followed by a bivariate NMA. The company used this for a scenario analysis in its model. The EAG highlighted several limitations with the company's updated NMAs including:

- the risk of bias and generalisability of included studies was not reported
- an NMA feasibility assessment was not done
- the impact of including new studies on between-study heterogeneity in updated NMAs was not reported.

The EAG stated that it was able to validate the company's baseline risk-adjusted NMAs but not the bivariate NMA or the 2-stage NMA (results of the NMAs are deemed confidential so cannot be reported here). The EAG preferred to use the 2-stage NMA in its base case, even though it had wide credible intervals. This was because this 2-stage analysis addresses most of the committee's concerns on adjustment of differential placebo response across studies and includes all relevant studies on IVIg and PLEX. The committee was aware that the bivariate NMAs used in the

company's base case did not adjust for differential placebo response across studies. But the committee noted that the results of the bivariate NMAs, including the odds ratios and associated credible intervals, presented at the third committee meeting (including 1 study on PLEX) were similar to those presented at the second meeting (which did not include the study on PLEX). The odds ratios of the bivariate NMAs were also similar to those of other NMAs presented at the third meeting including the 2-stage NMA. This meant that the 2-stage NMA that combined both bivariate and baseline risk-adjusted NMAs did not change the odds ratios much. The committee noted the wide credible intervals of the 2-stage NMA. On balance, the committee decided that the MG-ADL response rate informed by the bivariate NMAs at the third committee meeting was appropriate for decision making but there are uncertainties.

Economic model

Company's modelling approach

Company's original model

3.12 The company used a cohort state transition model to estimate the cost effectiveness of zilucoplan against the comparators. The model included 7 health states. People start in the 'uncontrolled' health state and transition to the 'response' health state if they meet the treatment response criteria (decrease of 3 or more in MG-ADL score) at the response assessment timepoint. Responders are further divided into 3 subhealth states: 'stable response' (MG-ADL score remains stable after time of response assessment), 'loss of response', and 'continued response' (MG-ADL score continues to improve after time of response assessment). The exact proportion who transition into each health state is considered confidential by the company and so cannot be reported here. Within each health state (except death), people in the model can transition to the 'exacerbation', 'myasthenic crisis', or 'death' states. The model has a cycle length of 2 weeks and a time horizon of 48.2 years. At the first

meeting, the committee considered that the model could be appropriate for decision making if it accounted for subsequent treatment use.

Company's revised model at the second committee meeting

3.13 After the first draft guidance consultation, the company submitted a revised economic model that included subsequent treatment use (see sections 3.15 and 3.16) and that also included several uncaptured benefits (see sections 3.20 to 3.22). In this revised model, the company assumed a proportion of people in the 'continued response' health state have reached minimal symptom expression (MSE), defined as an MG-ADL score of 0 or 1, which is used clinically as a treatment goal in gMG. The clinical expert explained that people who reach MSE have virtually no symptoms of gMG. They also explained that MSE is a clinically relevant outcome, and that both a reduction of 3 points or more in MG-ADL score (treatment response criteria in RAISE) and an MG-ADL score of 0 or 1 (MSE) are important outcomes to consider. The company stated that the MSE data for zilucoplan was from RAISE-XT (see section 3.7), so there is no MSE data for a placebo arm. The company also stated that, based on clinical opinion, it assumed that in the 'continued response' health state, MSE was reached by 10% of people having IVIg or PLEX but by no one having refractory standard treatment (corticosteroids and NSISTs; included as part of the subsequent treatment by the company [see section 3.15] at the second committee meeting). The proportion of people in the 'continued response' health state reaching MSE on zilucoplan was considered confidential by the company and so cannot be reported here. The company also assumed that people reaching MSE remain in the 'continued response' health state for the lifetime horizon of the economic model.

During the second committee meeting, the EAG noted that in addition to its impact on the transition probabilities of people moving into the 'continued response' health state, inclusion of MSE in the model also impacted on corticosteroid costs (see section 3.24) and utility decrement

associated with corticosteroid use in the model (see section 3.20). Given the lack of justification for the company's assumptions, the EAG preferred to revert to the patient distribution and health states that were used in the company's original economic model, without the inclusion of MSE. The committee noted that in the company's model, the transition from the 'uncontrolled' health state to the 'response' health state was originally based on people meeting the treatment response criteria. But with the data and information presented then, it was unclear how the data on MSE was used and implemented in the model. It also noted that the company assumed that no people on refractory standard treatment (corticosteroids and NSISTs) reached MSE in its base case, but 5% of people in the RAISE placebo arm reached MSE at week 12 during its randomisation period. This contradicted the company's assumption of no people on corticosteroids and NSISTs reaching MSE in the model. The committee also questioned the validity of the company's assumption that people who reached MSE were considered to be in the 'continued response' health state in the economic model for the entire time horizon of the model. This assumption was questionable because gMG is a condition characterised by relapse and remission and there was no evidence that zilucoplan or other treatments available for gMG can be considered curative.

The committee considered that MSE might be clinically relevant, but that it was not presented with sources of data for MSE or information on how MSE was implemented in the model. It requested the company to provide further information and additional evidence on:

- how transition probabilities were affected by MSE in the model
- its assumption on the proportions of people reaching MSE on zilucoplan, IVIg, PLEX, and corticosteroids and NSISTs only
- its assumption that, once reached, MSE endures for the lifetime of the economic model.

Company's revised model at the third committee meeting

3.14 In response to the second draft guidance consultation, the company stated that the MSE data was incorporated into its updated model submitted to the third committee meeting, by assuming people in the continued response health state have reached MSE. The proportion of people reaching MSE determines the distribution of people that respond to their initial treatment in the 'continued response (MSE)', 'loss of response' and 'stable response' health states. The proportion of people reaching MSE (the 'continued response' health state) on zilucoplan is based on data from RAISE-XT. Proportions for IVIg, PLEX and standard care (excluding IVIg and PLEX) reaching MSE are updated to be the averages taken from the clinical expert elicitation (n=4) conducted by the company during the second consultation (data are confidential so cannot be reported here). The company also explained that the benefit associated with MSE was further confirmed by the clinical expert elicitation. The EAG agreed that MSE is intuitively clinically relevant because it reflects the health state with minimal symptoms. But as noted in the company's clinical expert elicitation report, there was the caveat that MSE does not necessarily imply the absence of symptoms. This is because an MG-ADL score of 1 could be associated with symptoms that impact patients' quality of life. The EAG noted that there was no evidence from RAISE-XT suggesting the MSE in the zilucoplan arm would last for the lifetime of the economic model. It was also concerned with the uncertainties associated with the company's estimates for the proportions of people reaching MSE on IVIg, PLEX and standard care (excluding IVIg and PLEX in the company's estimate) in the model, which were informed solely by the clinical expert elicitation. This was because of the uncertainties associated with the methods of the expert elicitation (see section 3.16). During the third committee meeting, the committee questioned whether MSE means ongoing and long-term benefit like the company assumed in its model. One clinical expert explained that this matches their experience with people with refractory gMG in the past

5 years. The company explained that this assumption was applied in both arms, but the proportion of people reaching MSE was higher in the zilucoplan arm. The committee noted while MSE determines response status in the model and the transition from the 'continued response' to 'stable response' health states, the proportion of people in the 'loss of response' health state, which was also based on expert elicitation estimates, was the same for all treatments in both arms. The EAG explained that the proportion of MSE stays the same in the model, but it does not influence or connect to the 'loss of response' health state. This is also why time on treatment was largely similar despite a higher proportion of people on zilucoplan reaching MSE (see section 3.18). The committee understood that MSE may be clinically relevant, but it considered the company's assumption that reaching MSE leads to people remaining in the 'continued response' health state uncertain. It was concerned with the company's assumption that MSE would last for the lifetime of the model given the lack of evidence and the caveats noted by company's expert elicitation, which stated that MSE does not necessarily imply the absence of symptoms, that is an MG-ADL score of 1 could be accompanied by symptoms which could impact on health related quality of life. It was also concerned how MSE was implemented in the company's model because it does not connect to the 'loss of response' health state, nor impact time on treatment. Given these uncertainties, the committee considered that the company had not incorporated MSE into the model appropriately. It concluded that MSE should be removed from the model.

Subsequent treatments

3.15 The company's original model did not account for any future use of IVIg or PLEX for people who stop either zilucoplan or the comparators. Over time, people in the original model returned to the 'uncontrolled' health state, and only had corticosteroids and NSISTs. The committee recalled statements from the patient and clinical experts that gMG requires lifelong management. So, the committee thought it was implausible that someone with refractory gMG would stop zilucoplan and never have another

treatment other than corticosteroids and NSISTs. During the first committee meeting, the clinical experts noted that they would consider IVIg or PLEX for people who stop zilucoplan. They also explained that if a person's refractory gMG had not responded to a particular treatment, they would not use it again. So, there may be differences in the choice and proportion of subsequent treatments in the zilucoplan and comparator arms. The committee asked the company to account for subsequent treatments in the model.

In response to the first draft guidance consultation, the company accounted for subsequent treatments in its revised model submitted to the second committee meeting. It did this by applying the ongoing costs of the refractory 'basket' of standard care (see section 3.5) to the 'uncontrolled' health state, which people move to after stopping treatment or experiencing lack or loss of response to first-line treatment. The EAG questioned the appropriateness of the company's approach because it applied costs for IVIg and PLEX to the subsequent treatment for people who have already had first-line IVIg, PLEX or refractory standard treatment. But the EAG noted it is unclear whether people whose condition did not respond to first-line treatment would be offered the same treatment again. The EAG's approach instead assumed that people having IVIg as first-line treatment could have PLEX as subsequent treatment if response to IVIg is lost and vice versa. And if a treatment is offered once, it would not be used as a subsequent treatment again. It further noted that the company had not modelled any health benefits of the subsequent treatments in its revised model, only the costs.

During the second committee meeting, one clinical expert explained that, because of a lack of effective treatment options for gMG, people who have had IVIg or PLEX would likely be offered the most effective treatment as a subsequent treatment, even if they had this previously. The committee noted the divergent views about subsequent treatment. It also

noted the different approaches and assumptions taken by the company and EAG for modelling subsequent treatments. It noted there may be variations in subsequent treatment in practice and acknowledged the difficulties in modelling. It also noted that, if zilucoplan is recommended, the sequence of subsequent treatment for people who have had zilucoplan might differ from those who have only had IVIg, PLEX, or corticosteroids and NSISTs for their refractory gMG. The committee considered that it is inappropriate to model costs associated with subsequent treatments without also modelling treatment benefits. It therefore requested further information, and estimates for the proportion of people with refractory gMG who have:

- IVIg after IVIg
- PLEX after IVIg
- IVIg after PLEX
- PLEX after PLEX
- corticosteroids and or NSISTs only after IVIg
- corticosteroids and or NSISTs only after PLEX.

Subsequent treatments at the third committee meeting

3.16 In response to the second draft guidance consultation, the company adapted its model by accounting for both costs and benefits associated with subsequent treatments. The company also applied a weighted basket of subsequent treatments, including IVIg, PLEX and standard treatment only (corticosteroids and or NSISTs), to the 'uncontrolled off initial treatment' health state. The zilucoplan and 'basket' of standard care arm was each assigned an individual subsequent treatment basket. Different estimates for the proportion of people having subsequent IVIg, PLEX and standard care only (corticosteroids and or NSISTs) in the 2 arms were informed by the company's expert elicitation conducted during the second consultation (data is confidential so cannot be reported here). For the 'basket' of standard care arm, the proportion of people having initial IVIg, PLEX, and corticosteroids and or NSISTs at first line was informed by the

revised EAMS cohort (see section 3.5) in the company's base case. Also, people could have retreatment with the same treatment used first line in this arm. The EAG agreed that the company's weighted basket of subsequent treatment approach was reasonable. But for the 'basket' of standard care arm, the EAG used the overall EAMS cohort (see section 3.5) to inform proportion of people on initial IVIg, PLEX, and corticosteroids and or NSISTs only in its base case. The EAG also considered that the comparator basket should be applied consistently in both arms, and the proportion of people on subsequent IVIg, PLEX, and corticosteroids and or NSISTs only after zilucoplan should be the same as the proportion of people initially having IVIg and PLEX in the 'basket' of standard care arm. For the 'basket' of standard care arm, the EAG also noted that the company's clinical experts generally agreed that they would not re-treat with the same initial treatment. But there is no consensus among the clinical experts about the proportions of people having subsequent treatment when they switch treatment (for example, IVIg to PLEX or vice versa). There is also a wide range in estimates when switching between IVIg and PLEX. The EAG also noted NHS England's response to the second draft guidance consultation, which stated that using PLEX after IVIg for maintenance treatment is fairly infrequent, and using IVIg after PLEX is also very rare and only for people who are seriously ill. So the EAG preferred the lowest estimates from the company's expert elicitation for the proportion of people switching from IVIg to PLEX and vice versa in its base case (proportions are confidential and cannot be reported here).

During the third committee meeting, the company explained that there is a lack of evidence on subsequent treatment in refractory gMG, so it used clinical expert elicitation to inform its analysis. But it considered the EAG's estimate for people having subsequent corticosteroids and or NSISTs only in the 'basket' comparator arm unreasonably high (data are considered confidential by the company and so cannot be reported here). One of the

clinical experts explained that, provided there is no issue accessing PLEX, most people would switch to PLEX after stopping IVIg. Both clinical experts indicated that both the company and the EAG's estimates for the proportion of people on subsequent corticosteroids and or NSISTs only are higher than clinical practice. One clinical expert noted that the company's estimated proportion of having subsequent PLEX after IVIg was also higher than what would be seen in practice (data are considered confidential by the company and so cannot be reported here). The committee recalled its discussions on country-wide variations in access to IVIg and PLEX (see sections 3.4 and 3.5). It understood that PLEX is not available in many places, and there is limitation in use of IVIg. It questioned the variation in clinical practice in the UK. The clinical expert confirmed that their own practice may not represent that of other UK neurologists. The company explained that its analysis was informed by its expert elicitation, but indicated that the EAG had chosen the outlier of the estimate for switching between IVIg and PLEX (data is considered confidential so cannot be reported here) for its analysis. The EAG explained its estimate was also from the company's expert elicitation, and that NHS England's estimates are much lower. One of the clinical experts further noted that, because of limited access to IVIg in practice, it is difficult to have it regularly or switch from IVIg to PLEX and vice versa in practice. The committee noted the variations in access to IVIg and PLEX across the country and consequently the possible variabilities in switching between IVIg and PLEX in practice. The committee was aware that the cost-effectiveness estimates are highly sensitive to the proportion switching from IVIg to PLEX and vice versa. It understood this is an area where there is a lack of evidence. It recalled that both the company and EAG based their analysis on the company's expert elicitation, which had several uncertainties. These include:

- the lack of reporting of declaration of conflicts of interest of the recruited clinical experts

- it is unclear whether the clinical expert opinion is representative of UK MG centres
- the potential influence on clinical expert responses depending on the method of expert elicitation (individually or as a group)
- some results reported quantitatively may lack accuracy given some clinical experts found it difficult to answer some questions
- not all clinical experts were able to respond to all questions.

The committee noted that zilucoplan is an add-on to standard treatment, so it adds an additional line to the treatment pathway. Taking into account the uncertainty in the analysis, variations in access to IVIg and PLEX in practice, the estimates provided by NHSE, and the estimates based on the company's expert elicitation which are quite different, the committee considered that the EAG's preferred estimate (which is in between that of NHSE's and the company's) for the proportion switching from IVIg to PLEX and vice versa was reasonable to inform decision making. It further concluded that the EAG's approach is appropriate to model subsequent treatment, specifically:

- The overall EAMS cohort should be used to inform the proportion of people on initial IVIg, PLEX, and NSISTs and or corticosteroids only in the 'basket' of standard care arm.
- The 'basket' of standard care arm should be applied consistently in both arms: the proportion of people on subsequent IVIg, PLEX, and corticosteroids and or NSISTs only in the zilucoplan arm should be the same as the proportion of people initially having IVIg and PLEX in the 'basket' of standard care arm.
- The EAG's estimate for the proportion of people switching from IVIg to PLEX and vice versa in the 'basket' of standard care arm was reasonable but there are uncertainties
- If used once, the same treatment would not be used again as subsequent treatment.

Response assessment timepoint

3.17 The company selected the response assessment timepoint from the zilucoplan and the efgartigimod trials (12 weeks and 10 weeks, respectively), and used an assumption for IVIg and PLEX (6 weeks). The EAG noted that it had received clinical advice that treatment effects are seen much earlier, after 1 to 2 weeks, and response is often assessed 3 to 4 weeks after starting IVIg or PLEX. It also noted that later response assessment may mean someone's gMG responds and then that response is lost. The EAG chose to use a response assessment timepoint of 3 weeks for all treatments in the model. The clinical experts at the committee meeting agreed that they would typically assess a person who had IVIg or PLEX after 2 to 4 weeks. The committee concluded that a response assessment timepoint of 3 weeks reflected NHS practice, and the company implemented this in its revised model.

Time on treatment

3.18 In the company's revised model submitted during the first draft guidance consultation and critiqued by the EAG, the company assumed a maximum treatment duration of 2 years for all people on all treatments. The company also assumed that, after stopping zilucoplan, IVIg or PLEX, people will maintain the health improvements for the rest of their lifetime, with no ongoing costs. The EAG stated that a stopping rule was not included in the company's original model. It also considered that the company's assumption was not appropriate because gMG is a chronic condition that requires lifelong treatment, and the treatments are not curative. So the EAG removed this stopping rule from its base case but noted that clinical advice on the appropriateness of the company's 2-year stopping rule would be helpful. During the second committee meeting, the company explained that it had removed the stopping rule from another version of the model it also submitted during the consultation, but it was too late for the EAG to critique this. The committee noted that because zilucoplan is a new treatment, time on zilucoplan may differ from that of

the ‘basket’ of standard care, and this may impact the subsequent use of treatment including IVIg, PLEX, and corticosteroids and NSISTs. The committee would like the company to provide scenario analyses that explore a range of time on treatment assumptions for zilucoplan and treatments in the ‘basket’ of standard care.

During the second draft guidance consultation, the company did a scenario analysis using the transition probability to the ‘loss of response’ health state as a proxy to model time on treatment. The EAG considered the company’s proxy approach reasonable but noted that the times on treatment for zilucoplan, IVIg, and PLEX were similar in the company’s analysis (exact mean time on treatment is confidential and cannot be reported here). It questioned whether this would reflect clinical practice because zilucoplan is a well-tolerated and easy to administer treatment compared with IVIg and PLEX. During the third committee meeting, the committee questioned time on treatment for zilucoplan being very similar to time on treatment for IVIg and PLEX, despite a larger proportion of people reaching MSE in the zilucoplan arm in the company’s model (see section 3.14). The company explained that time on treatment was solely based on “loss of response rate” in the model, so time on treatment was similar across treatments. However, the committee noted the company’s revised proportion of people reaching MSE (continued response) on IVIg or PLEX, which was based on the expert elicitation conducted during the second draft guidance consultation (see section 3.14), was only half of that for zilucoplan in the company’s model, yet the time on treatment was similar for zilucoplan, IVIg and PLEX. It questioned whether this was reasonable. The EAG explained that MSE affects the transition probability between the ‘continued response’ and ‘stable response’ states only (see section 3.14), but does not connect to the ‘loss of response’ state in the model. This is because the proportion of people staying in the ‘loss of response’ state was the same for all treatments (the exact proportion of people in the ‘loss of response’ state is confidential so cannot reported

here). The committee recalled its discussion on the uncertainties around the MSE assumptions, and its concerns about how MSE was implemented in the company's model (see section 3.14). Considering the counterintuitive similar estimates for time on treatment across treatments, the uncertainties around assumptions for MSE and how it was modelled, the committee concluded that there is substantial uncertainty with time on treatment and this should be estimated with MSE removed from the model.

Utility values

3.19 Health-related quality of life data was captured in RAISE through the EQ-5D-5L. EQ-5D-5L scores were mapped to the EQ-5D-3L in line with the NICE reference case. Utility values based on EQ-5D scores from RAISE were used in a regression model and fitted for all people in the trial. Changes in utility depended on the person's baseline EQ-5D score, MG-ADL score and body mass index. The model applied disutilities for exacerbations and myasthenic crises, sourced from the REGAIN trial for eculizumab. The model did not apply disutilities for adverse events, because the company noted that there were no serious adverse events with an incidence of 5% or more in RAISE. The company's original model also did not apply disutilities for carer burden. At the first meeting, the committee considered that there may be several uncaptured benefits associated with zilucoplan and asked the company to provide scenarios that consider these.

Utility decrements for corticosteroid use

3.20 In response to the first draft guidance consultation, the company accounted for some of these uncaptured benefits in its revised model. The company explained that high corticosteroid use has a substantial impact on quality of life, and that it can lead to severe complications such as diabetes, osteoporosis, depression and infection. It explored the impacts of corticosteroid use for people with uncontrolled gMG by assuming that zilucoplan has steroid-sparing benefits. Referencing data from RAISE and

RAISE-XT, the company considered that people having zilucoplan can reduce or stop their use of corticosteroids, while maintaining disease control. The company suggested that the EQ-5D may not be sensitive enough to measure the utility impact of corticosteroid use. So the company applied a utility decrement of 0.18 to the 'uncontrolled' health state for people on a high dose of corticosteroids (10 mg/day or more), and a utility decrement of 0.07 to the 'stable' health state for people on a low dose of corticosteroids (below 10 mg/day). Because of a lack of data on the utility decrements associated with refractory gMG, these were instead based on people with systemic lupus erythematosus in the UK. The EAG removed utility decrements associated with corticosteroid use from its base case because it considered this a double counting of what has been captured by the EQ-5D. The committee considered that it is uncertain if the EQ-5D had captured all the utility decrements associated with corticosteroid use. It also noted that further evidence and assumptions, beyond what the company has considered, are needed to account for this quantitively in the model, but these had not been presented.

In response to the second draft guidance consultation, the company considered disutility for corticosteroid use should be included quantitatively. It noted that it was unlikely that utility decrement associated with corticosteroid use is captured in EQ-5D scores. And given the paucity of data in gMG, data on systemic lupus erythematosus in the UK from Sullivan et al. (2017) and in Sweden from Bexelius et al. (2013) had been used as a proxy to quantitatively estimate utility impact of steroid use in its updated analysis. It also noted that the utilities from the regression analysis (see section 3.20) came from RAISE, before the full steroid-sparing effect of zilucoplan has been captured. Applying these utilities will not be reflecting the benefit of reducing the dose or discontinuing steroid treatment at any timepoint so the disutility bridges this gap. The EAG did not comment further on the company's response but excluded

corticosteroids disutility from its base case. The committee remained uncertain about whether EQ-5D had captured all the utility decrements associated with corticosteroid use. It also noted that the company's estimates used in the model were based on people with systemic lupus erythematosus, which is a different condition to gMG. The committee noted it had not been presented with additional robust evidence to inform the corticosteroid utility decrement quantitatively in the economic model. It concluded that it would consider utility decrement associated with corticosteroid use qualitatively in its decision making.

Utility increment for mode of administration

3.21 In its revised economic model, the company also applied a utility increment of 0.05 per administration to account for the quality of life benefit of subcutaneous self-administration of zilucoplan compared to in-hospital administration of IVIg and PLEX. The EAG noted that the studies referenced by the company to support the inclusion of this utility increment related to other conditions (Gaucher disease, bone metastases, pulmonary arterial hypertension, transfusion-dependent beta-thalassaemia and haemophilia A) rather than gMG. These studies referred to different modes of administration other than subcutaneous injection (for example, oral administration, infusions) so the EAG preferred to remove this utility increment for subcutaneous self-administration of zilucoplan from its base case. The committee agreed that it was more appropriate to consider that the benefits of at-home administration are from the implied avoidance of in-hospital administration of IVIg and PLEX, and the associated impacts that these treatments often have on quality of life. It therefore considered that, if appropriate to include, this uncaptured benefit should be incorporated as a utility decrement for IVIg and PLEX, rather than a utility increment for zilucoplan.

In response to the second draft guidance consultation, the company removed the administration utility benefit for zilucoplan. Instead it estimated a per-model cycle disutility of IVIg and PLEX administrations

calculated by weighting the number of IVIg and PLEX infusions per model cycle (disutility values are confidential and cannot be reported here). In the absence of data to inform the disutility values for IVIg and PLEX in gMG, the disutility values are derived from Johnston et al. (2021), a study assessing utility impact of intravenous infusion in haemophilia A, and the same disutility for IVIg is applied to PLEX. The EAG highlighted that there is a lack of evidence presented by the company to show that haemophilia A is an appropriate proxy for gMG. The EAG also noted that it is unclear how the disutilities were calculated from Johnston et al. (2021). It explained that in this study the utility data was derived from a vignette-based time trade-off exercise in Canadian adults without haemophilia, with a small sample size (n=82). So the EAG did not include the disutility associated with IVIg and PLEX in its base case. During the third committee meeting, the committee questioned how the company estimated per cycle disutility associated with IVIg and PLEX that combined consequences of frequent venous access and recurrent bleeds caused by haemophilia. The company explained that there is a lack of evidence in gMG to inform disutilities associated with IVIg and PLEX. It explained that the Johnston et al. study informs the disutility associated with a single intravenous or subcutaneous infusion. This was then multiplied by the number of IVIg or PLEX administrations per cycle to derive the disutility for IVIg and PLEX. The company acknowledged the limitations associated with using Johnston et al., particularly that haemophilia A cannot be compared with gMG. But it explained that the disutility is derived based on the intravenous or subcutaneous infusion component and not bleeds associated with haemophilia A. This is because it adjusted for bleeding in the regression analysis. The patient expert highlighted the negative impact of cannulation, particularly with PLEX, and long hospital stays. The committee considered that despite the limitations in the company's approach to estimate the disutility associated with IVIg and PLEX, it is important to consider this in the economic modelling. It noted the uncertainties but considered that the company's

approach using Johnston et al. was reasonable. The committee concluded that it is appropriate to include the disutility associated with IVIg and PLEX in the economic model.

Carer utilities

3.22 In its revised economic model, the company also explored the inclusion of carer benefits from zilucoplan use, because gMG is associated with a substantial carer burden. Carer utility decrements were sourced from a study in multiple sclerosis (Acaster et al. 2013), and these were included in the model as scenarios. The EAG explained that it had not seen evidence that multiple sclerosis is a suitable proxy for gMG, and that the committee for the NICE technology appraisal of efgartigimod for treating gMG had concluded that carer utility decrements should be excluded from the economic model. It therefore agreed with the EAG that these scenarios were inappropriate to include in the base-case analysis. The committee considered it appropriate to take into account the impact of zilucoplan on carers qualitatively in its decision making.

Costs

Resource use

3.23 The company's model applied treatment costs for IVIg every 3 weeks and for PLEX every 4 weeks. The EAG received clinical advice that, in the NHS, IVIg and PLEX are typically given every 4 to 8 weeks, with the interval between treatments sometimes extended to 12 weeks or, rarely, 16 weeks. The clinical experts noted that treatment intervals of 8 weeks or longer are not common and that 4 weeks is typical. The company also assumed that the PLEX administration cost was equal to the administration cost of subcutaneous immunoglobulin. The EAG disagreed, preferring to use the NHS reference cost SA44A – Single Plasma Exchange (£910). The committee concluded that IVIg and PLEX costs should be applied every 4 weeks and that the NHS reference cost for

PLEX should be used. The company included this change in its revised economic model.

Corticosteroid costs

3.24 In its revised model, the company updated costs for corticosteroid use. There was no data reported in the literature for the costs of corticosteroid use related to dose for people with gMG, so the company used costs for corticosteroid use in systemic lupus erythematosus (a proxy condition). The EAG explained that the costs of managing adverse clinical outcomes from corticosteroid use had already been incorporated into the company's original economic model for the first committee meeting. The EAG further noted that the committee for the NICE technology appraisal of efgartigimod for treating gMG had accepted a weighted average of NHS reference costs for intolerable adverse events, reported in Lee et al. (2018), to estimate corticosteroid complication costs associated with gMG. The committee considered that it would like to see the costs from Lee et al. explored and the company agreed to use these in future analyses.

In response to the second draft guidance consultation, the company did a scenario analysis using costs of corticosteroids from Lee et al, while using Stirnadel-Farrant et al. (2023) to inform corticosteroid costs in its base case. It highlighted the several limitations with Lee et al., including:

- absence of data on adverse events for people not having corticosteroids
- the severity of adverse events is not specified
- costs according to corticosteroid dose were not included.

The EAG highlighted that the NICE committee for efgartigimod accepted using data for intolerable side effects caused by corticosteroid use from Lee et al. as the source of the costs of managing corticosteroids. It further explained that the Lee at al. data is for people with gMG, whereas Stirnadel-Farrant et al. reports costs for people with

systemic lupus erythematosus. So the EAG used Lee et al. data to inform the corticosteroid costs in its base case. The EAG also highlighted that the company had not added the costs for corticosteroids for people reaching MSE in the 'continued response' health state in the zilucoplan arm, but added these costs for people reaching MSE for IVIg and PLEX. So for consistency the EAG added costs for corticosteroid management for people reaching MSE in the zilucoplan arm. The committee thought that the EAG's approach to add corticosteroid management costs to all treatments equally, including for people reaching MSE, was appropriate. It concluded that corticosteroid costs informed by Lee et al. and applied equally in the zilucoplan arm and the 'basket' of standard care arm in the economic model is appropriate.

Use of IVIg and SCIg

3.25 The company's original model assumed that 50% of people had IVIg and 50% had SCIg, while its revised model assumed that 100% of people had IVIg. The EAG considered the company's original assumption to be appropriate and included it in its base case. But the clinical expert confirmed that SCIg is rarely used for treating refractory gMG. The committee concluded that 100% of people having IVIg in the economic model was appropriate.

Uncertainties

3.26 The committee noted the high level of uncertainty in the evidence and modelling, specifically:

- the company's definition of refractory (see section 3.3) and the definition of refractory in the EAMS cohort, which was further revised by the company to inform the proportion of people on treatment in the 'basket' of standard care (see section 3.5)
- the company's NMAs (see sections 3.9 to 3.11)
- how MSE was implemented in the model including:

  - sources of data that informed MSE
  - the uncertainty around how MSE affects the transition probabilities between 'continued response' and 'stable response' but does not connect to 'loss of response'
  - the assumption that MSE would last for the lifetime of the model despite lack of evidence (see sections 3.13 and 3.14)
- assumptions on subsequent treatments (see sections 3.15 and 3.16)
- the disutility value for IVIg and PLEX in the model (see section 3.21)
- the company's assumed extra utility decrement associated with corticosteroid use in the model (see section 3.20)
- the extra costs associated with corticosteroid use in the model (see section 3.24).

Committee's preferred assumptions

3.27 The committee's conclusions and preferred assumptions included:

- that the company's revised target population specifying 2 or more NSISTs is appropriate (see section 3.3)
- that 'basket' of standard care is the appropriate comparator, with some people having IVIg, some having PLEX, and some having neither; everyone should have corticosteroids and NSISTs (see section 3.4)
- using the overall EAMS cohort to inform the proportion of people on treatment in the 'basket' of standard care (see section 3.5)
- that the results of the whole trial populations of RAISE and RAISE-XT can be generalised to those who would have zilucoplan in the NHS (see sections 3.6 and 3.7)
- using bivariate NMAs to inform response rate in the model (see sections 3.9 to 3.11)
- removing MSE from the model (see sections 3.13 and 3.14)
- estimating time on treatment with MSE removed from the model (see section 3.18)

- using the EAG's approach of modelling subsequent treatment (see sections 3.15 and 3.16)
- that the response assessment timepoint should be 3 weeks for all treatments (see section 3.17)
- taking utility decrement associated with corticosteroid use into account qualitatively (see section 3.20)
- including the disutility associated with IVIg and or PLEX use in the model (see section 3.21)
- Excluding carer disutility from the model and taking this into account qualitatively (see section 3.22)
- applying the costs of IVIg and PLEX every 4 weeks, and using the NHS reference cost for PLEX administration (see section 3.23)
- using Lee et al. (2018) to inform corticosteroid costs in the model (see section 3.24)
- that the assumed use of IVIg should be 100% because SCIg is rarely used for treating refractory gMG (see section 3.25).

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.28 Because of confidential commercial arrangements for zilucoplan and some of the comparators, the exact cost-effectiveness results are confidential and cannot be reported here. Although some of the company's incremental cost-effectiveness ratios (ICERs) in some analyses were within the range NICE normally considers to be a cost-effective use of NHS resources, they did not include the committee's preferred assumptions. The EAG's base-case ICER was substantially above this range.

Acceptable ICER

3.29 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of

NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high uncertainties associated with the assumptions on MSE, subsequent treatment and time on treatment in the model (see sections 3.13 to 3.16 and section 3.18). But the committee was also aware that refractory gMG is a rare condition with high unmet need, and noted the potential challenges in generating robust evidence to support the company's assumptions in the model. It also noted there may be uncaptured benefits associated with zilucoplan in reducing corticosteroid use (see section 3.20) and carer disutilities (see section 3.22). And, if recommended, variation in access to zilucoplan may be less an issue compared with that for IVIg or PLEX (see section 3.30). So the committee agreed that, despite the high uncertainties, the maximum acceptable ICER would be at the upper end of the range that NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Using the committee's preferred assumptions for the comparison with the 'basket' of standard care resulted in ICERs that were well above the range considered a cost-effective use of NHS resources. This is even when taking into account the unmet needs, potential uncaptured benefits associated with zilucoplan in the model, and the consideration that, if recommended, zilucoplan may reduce variation in access to treatment for refractory gMG. The committee recognised that the model estimates a modest QALY benefit, and because zilucoplan is an addition to the treatment pathway which is associated with substantial additional costs. This in effect generates a very high ICER. So, the committee concluded that zilucoplan is not recommended for routine commissioning for treating refractory gMG.

Other factors

Equality

3.30 The committee considered that gMG may have a different burden on women than men. gMG is more prevalent in women, women are typically younger at disease onset, and women typically have higher mortality. Furthermore, pregnancy may contraindicate some types of treatment. It also noted that some people with certain religious beliefs may not be able to have IVIg or PLEX because they cannot have blood products but they would be able to access complement inhibitor treatment. It noted that sex, pregnancy and religion are protected characteristics under the Equality Act 2010. The committee also heard that patients living away from centres with MG experts may not have access to zilucoplan. This will be even more concerning in people from lower socioeconomic classes. Therefore, educating patients and doctors will be crucial to ensure avoiding unlawful discrimination against patients that are geographically away from large centres. The committee considered these equality issues, and agreed that its recommendations would not have a different impact on people protected by the equality legislation than on the wider population. The committee agreed that if zilucoplan was recommended, the decision to use zilucoplan during pregnancy should be made by the person and their clinician if the clinical benefit outweighs the risks. The committee also noted that access to specialist centres is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation. But the committee agreed with the patient expert at the third committee meeting that, if recommended, access to zilucoplan could potentially reduce health inequality. No other potential equalities issues were identified.

Uncaptured benefits

3.31 The committee considered if zilucoplan was innovative. During the first committee meeting, the patient experts clearly noted that treatment with IVIg or PLEX was time-consuming, requiring regular hospital stays. They

thought that zilucoplan, as a subcutaneous treatment that can be taken at home, would be much more convenient and could improve adherence. The clinical experts noted how resource intensive IVIg and PLEX are to administer. They also explained that people who have zilucoplan may be able to reduce their corticosteroid dose. This could lead to fewer corticosteroid-related complications. Both patient and clinical experts considered that zilucoplan has advantages for patients, carers, and healthcare professionals. Considering the entirety of the evidence and uncertainty involved, the committee concluded that it would consider the additional utility decrements associated with corticosteroid use and the impact of zilucoplan on carers qualitatively in its decision making (see section 3.20 and section 3.22).

Conclusion

Recommendation

3.32 The committee concluded that, given its preferred assumptions and based on the analysis it had seen, the cost-effectiveness estimates were highly likely to be substantially above the top end of the range that NICE considers a cost-effective use of NHS resources. The committee noted there were some uncaptured benefits but, given the magnitude of the most likely ICER, these were not sufficient to offset this. The committee concluded that zilucoplan could not be recommended for treating antibody-positive gMG in adults.

Evaluation committee members

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

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

Dr Charles Crawley

Chair, technology appraisal committee B

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.

Tom Palmer, Luke Cowie and Zain Hussain

Technical leads

Eleanor Donegan and Yelan Guo

Technical advisers

Jeremy Powell

Project manager

Emily Crowe

Associate director

ISBN: [to be added at publication]