NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Zilucoplan for treating antibody-positive generalised myasthenia gravis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using zilucoplan 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?

Issue date: November 2024

Note that this document is not NICE's final guidance on this technology. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using zilucoplan in the NHS in England.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: 5 December 2024
- Second evaluation committee meeting: TBC
- Details of the evaluation committee are given in section 4

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 immunosuppressants. 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 standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone. But zilucoplan has not been compared with plasma exchange and there is uncertainty in the indirect treatment comparisons between zilucoplan and intravenous immunoglobulin. So it is unclear how well it works compared with these treatments.

As well as the uncertainties in the clinical evidence, there are substantial uncertainties in the economic model. It is not possible to determine a likely cost-effectiveness estimate for zilucoplan. So, zilucoplan is not recommended.

Issue date: November 2024

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 3.7), 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 agreed 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 (see section 3.6).

Comparators

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

- standard care without zilucoplan (including corticosteroids and immunosuppressants, 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 meeting (13 June 2024), 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 immunosuppressants. So, corticosteroids and immunosuppressants 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 immunosuppressant 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 immunosuppressants), some have PLEX (plus corticosteroids and immunosuppressants), and some have corticosteroids and immunosuppressants only.

The EAG assumed that data on the proportion of people having each treatment from the efgartigimod Early Access to Medicines Scheme (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 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; Dionísio et al. 2024). 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 immunosuppressants)
- 14.6% were having long-term PLEX (plus corticosteroids and immunosuppressants)
- 41.6% were having only corticosteroids and immunosuppressants.

Company's revised 'refractory standard care'

3.5 During 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 (see section 3.14). The company disagreed with the EAG's preference for using the 'basket' of standard care as the comparator. This is because it considered that zilucoplan would displace IVIg and PLEX for people with refractory gMG that has not responded to corticosteroids or immunosuppressants. It also considered that the 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 immunosuppressants 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 original EAMS cohort (n=48) and comprised:

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

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, and 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 its preference to use this to model the proportions of subsequent treatments that people would have after zilucoplan (see section 3.14).

Committee conclusion on comparators

3.6 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 tolerated, and that was being regularly managed with IVIg and PLEX. But, the committee noted that there was no definite inclusion criteria for the EAMS and there may have been different thresholds for inclusion depending on clinical experience or access to infusion centre facilities. It also remains unclear how refractory gMG was defined for the EAMS or by the company.

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 immunosuppressants should be included in both arms. The committee considered whether or not the revised efgartigimod EAMS cohort would be more similar to the zilucoplan target population which was based on the pre-planned refractory subgroup of RAISE. The committee noted that there is variation in how refractory populations have been defined in RAISE and the EAMS cohort, and that there remains considerable uncertainty about which definition of refractory gMG is more appropriate for the target population for zilucoplan. The committee was also 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 noted the very small sample size of the EAMS cohort and considered that it had not been presented

with sufficient justification for the company's revised EAMS proportions. The committee concluded that it would like the company to clarify the target population for zilucoplan and to provide further evidence and rationale to support its preference for a revised EAMS cohort to inform its preferred basket of refractory standard care.

Clinical effectiveness

RAISE

3.7 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 immunosuppressants. 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 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

3.8 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

3.9 In its submission, the company positioned zilucoplan for people with refractory gMG. 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 3.10), 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 considered 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. 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

3.10 The company did NMAs to estimate the comparative effectiveness of zilucoplan with the comparators. In its original evidence submission, the company did NMAs for several outcomes, but the only outcome used in the economic model was MG-ADL response. The MG-ADL response NMA compared zilucoplan and efgartigimod, connected through the common placebo comparator. IVIg or PLEX studies were not included in this NMA because none reported the MG-ADL response outcome. The results of the NMAs are considered confidential by the company and so cannot be reported here.

The EAG had several concerns with the company's original NMAs. It noted differences in baseline characteristics and placebo response rates

between RAISE and the efgartigimod trial. The NMAs did not account or adjust for these differences. Also, the EAG was 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. The EAG previously asked the company to try different methods, such as a matching-adjusted indirect comparison (MAIC), but the company declined to do so. The company explained that it had assessed the feasibility of doing an adjusted NMA but concluded that it was not possible because of the small number of studies identified. It also explained that a MAIC would be limited by heterogeneity in reporting across trials and by small sample sizes after population matching.

At the first meeting, the committee 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 using different methods to obtain estimates of relative differences in those studies so that IVIg and PLEX could be included. The committee considered that there were multiple issues with the NMA that meant that the comparative effectiveness of zilucoplan was highly uncertain. So, it asked the company to provide additional analyses that (see section 3.32):

- use data from more of the identified studies, particularly for IVIg and PLEX
- consider outcomes other than MG-ADL response rate to produce estimates of relative effectiveness
- account and adjust for the differential placebo response observed in the trials
- maintain randomisation.

Revised indirect treatment comparisons

3.11 To address the committee's and EAG's concerns, the company provided new indirect treatment comparisons in its response to the first draft

guidance consultation. These new analyses included baseline risk-adjusted NMAs, unanchored MAICs and a bivariate NMA.

The company did baseline risk-adjusted NMAs that assessed the probable impact of the differences in placebo response across studies. The EAG commented that these NMAs adjusted for heterogeneity of placebo responses across studies. But, it noted that that these analyses did not include data for IVIg and do not inform the economic model.

The company also did 2 unanchored MAICs of zilucoplan versus IVIg on the outcome of proportion of people with worsening QMG score (4 points and more) from baseline, and on QMG score and QMG response rates at 2 and 4 weeks (with another additional study by Bril et al. (2023) included in the analysis for this outcome). These outcomes could not be included in any of the other NMAs because of a lack of link to the network, or because relevant outcomes were not reported. The company explained that despite data limitations causing uncertainty (shown by the wide credible intervals across the NMAs), the point estimates across the different unanchored MAICs were broadly similar. 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 presented a bivariate NMA for the MG-ADL outcome and used QMG outcomes to enable estimation of MG-ADL when this outcome was missing. One additional study comparing IVIg with placebo was also included in this NMA. The results of the bivariate NMA were used to inform the economic model. 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 retained its approach of using a referent placebo response rate adjustment (see section 3.15) to adjust for placebo response differences across the

included trials. The committee noted that the referent placebo response rate calculation was intended to adjust for placebo response heterogeneity, but that it would have been preferable to account for this 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. The EAG noted that no studies on PLEX had been identified and so the relative effectiveness of zilucoplan against PLEX remained highly uncertain. The EAG further commented that the company was not transparent about how it extended its original search or screening eligibility criteria, so it remains uncertain whether any further evidence, particularly for PLEX, could be available.

The committee noted that although no study on PLEX was included in the NMAs, the company had derived the response rate for PLEX from the Barth et al. (2011) study that compared IVIg and PLEX (see section 3.15). The company explained that the Barth et al. study was not included in the NMAs because the networks were linked by placebo as the common comparator, but there was no placebo arm in Barth et al. The EAG noted that, in theory, it was possible to include the Barth et al. study in the NMAs by using IVIg as the common comparator. The committee noted that the bivariate NMA provided by the company was an improvement over its previous NMA because it allowed the inclusion of an additional study of IVIg versus 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. It concluded that there were still substantial uncertainties in the NMAs and so the effectiveness of zilucoplan relative to IVIg and PLEX remained unclear. It was aware of the limitations with Barth et al. (see section 3.15), but given the lack of evidence, it requested that the company:

- explore linking the networks by using IVIg as the common comparator instead of placebo

- provide statistical codes for the NMAs to the EAG for verification
- adjust for differential placebo response as well as baseline population characteristics across studies included in the NMAs
- incorporate the uncertainties from the NMAs into the model.

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

3.13 After the first draft guidance consultation, the company submitted a revised economic model that attempted to account for subsequent treatment use (see section 3.14) and that also included several uncaptured benefits (see sections 3.20 to 3.22). In this revised model, a proportion of people in the 'continued response' health state were assumed to 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. The company stated that the MSE data was from RAISE-XT (see section 3.8), 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 care treatment (corticosteroids and NSISTs; considered as part of the subsequent treatment by the company [see section 3.14]). The proportion of people in the 'continued response' health state reaching MSE on zilucoplan is considered confidential by the company and so cannot be reported here. The company explained that people reaching MSE remain in the 'continued response' health state for the lifetime horizon of the economic model. The committee noted that this assumption is highly uncertain because gMG is a condition characterised by relapse and remission and that none of the treatments available for gMG can be considered curative.

The EAG highlighted that it was unable to revert the company's revised base-case results to the original version the company had submitted for the first committee meeting. On the inclusion of MSE data in the model, the EAG commented that this is an alternative way of using MG-ADL scores to model the benefits of zilucoplan against the comparators. It noted that the company did not sufficiently justify this alteration to the model, and that it was uncertain whether the inclusion of MSE is clinically appropriate. Because of this, 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. During the second committee meeting, the clinical expert 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 committee

recalled 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, it is unclear how the data on MSE was used and implemented in the model. The committee was also aware that the company's MSE data for zilucoplan was from RAISE-XT which had a longer follow up compared with the 12 weeks follow up in RAISE. It noted that the company assumed that no people on refractory standard care treatment (considered to be corticosteroids and NSISTs) reached MSE in its base case, but 5% of people in the RAISE placebo arm had MSE at week 12 during its randomisation period. During the second committee meeting, the EAG also explained that the inclusion of MSE in the model also impacts on corticosteroid costs (see section 3.24) and utilities associated with corticosteroid use in the model (see section 3.20). This is in addition to its impact on the transition probabilities of people moving into the 'continued response' health state. The committee noted that it was not presented with information on how transition probabilities in the model are affected by MSE and this was unclear. The EAG further noted that, in the company's revised model, people on zilucoplan reaching MSE would not incur corticosteroid costs, but people on IVIg or PLEX incur corticosteroid costs even when MSE is reached. The committee concluded 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:

- information on how transition probabilities are affected by MSE in the model
- additional evidence to inform estimates of the proportion of people reaching MSE on zilucoplan
- information around the proportion of people reaching MSE in the RAISE placebo arm
- further details and justification for its assumptions on the proportion of people reaching MSE on IVIg and PLEX

- further details and justification for its assumptions on the proportion of people reaching MSE on refractory standard care treatment (corticosteroids and NSISTs).

  It further noted that, once reached, MSE endures for the lifetime of the economic model. The committee considered that this has a substantial impact on the cost effectiveness of zilucoplan. It concluded that it would like to see further evidence and justification to support this assumption.

Subsequent treatments

3.14 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 immunosuppressants. 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 immunosuppressants. 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 did not previously respond 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 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. 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 company considers this a conservative approach. 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 care. 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 won't be used as a subsequent treatment again.

The EAG explained that the costs associated with the subsequent treatment have a significant impact on the costs for people in the 'uncontrolled' health state, leading to a substantial increase in total costs for all treatments in the company's revised model. It also explained that people having IVIg may switch to PLEX and vice versa, but that there is no information available to inform the proportions doing this in the company's refractory basket of standard care treatments in its revised model. 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, the clinical expert also 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 noted that currently there is a lack of clear understanding on the use of subsequent treatment after people with refractory gMG stop IVIg, PLEX, or corticosteroids and NSISTs in the NHS. It also noted that, if zilucoplan is recommended, the sequence of subsequent treatment for people after zilucoplan might differ from those

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who have only had IVIg, PLEX, or corticosteroids and NSISTs for their refractory gMG. The committee concluded that it is inappropriate to model costs associated with subsequent treatments without also modelling treatment benefits. It requested further information, particularly from NHS England and the company, on the routine practice for subsequent treatment in the NHS. It also requested 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.

Treatment response rates

3.15 In its original model, the company used the NMA results to estimate the MG-ADL response rates for zilucoplan and efgartigimod. The company converted the odds ratios of zilucoplan compared with placebo, and efgartigimod compared with placebo, into relative risks. Then, the relative risks were applied to the referent response rate. The referent response rate was calculated as the average placebo response rate across studies identified in the NMA. The company considers the response rates for zilucoplan and efgartigimod, and the referent response rate, to be confidential and so they cannot be reported here. IVIg or PLEX response rates in the company's original model were based on data from Barth et al. (2011), a Canadian randomised controlled trial of 84 people with gMG who had either IVIg or PLEX. In its original submission, the company back-calculated the odds ratios for IVIg and PLEX from Barth et al., before using the same methodology to convert to relative risks and response rates, as with zilucoplan and efgartigimod. The calculated response rates were 51% (IVIg) and 57% (PLEX). The EAG noted several limitations with using data from Barth et al., including that:

- the population was not explicitly defined as refractory
- MG-ADL data was not available, so the response was defined as a 3-point or more improvement in QMG
- no confidence intervals or standard errors were provided with the response rates.

Because of these uncertainties, the EAG chose to use the unadjusted response rates from the zilucoplan and efgartigimod trial arms of 73.1% and 73.0%, respectively. For IVIg and PLEX, the EAG received clinical advice that the expected response is much higher than estimated using Barth et al., with approximately 70% of people with gMG in clinical practice having a response. So, the EAG preferred to use the 70% MG-ADL response for both IVIg and PLEX. During the first committee meeting, the clinical experts noted that they expect about two-thirds of people with gMG who have IVIg or PLEX would have an MG-ADL response, and so considered 70% plausible. The committee considered that there was uncertainty in the estimates of the comparative effectiveness of zilucoplan. It noted that the company's approach used results from the uncertain NMA, and estimated IVIg and PLEX response from a study with several limitations. The committee also noted that the EAG's approach did not adjust for the placebo response observed in both RAISE and the efgartigimod trial. It noted that it would prefer response rates to be based on clinical data rather than expert opinion. The committee asked the company to provide more analyses to clarify this.

Revised response rates

3.16 In response to the first draft guidance consultation, the company revised its economic model. The estimate for the referent response rate was calculated as the overall mean of log odds based on individual log odds for each study reporting MG-ADL instead of the average placebo response rate across studies identified for the bivariate NMA. The referent response rate is considered confidential by the company and cannot be

reported here, but the company noted that the outcomes from both calculations are very similar. It also updated the treatment response rates in the model calculated as follows, specifically:

- Response rates for zilucoplan and for IVIg were each calculated by using the odds ratio for zilucoplan and IVIg against placebo from the bivariate NMA (see section 3.11), converted into relative risks, then applied to the referent response rate. The response rates for zilucoplan and IVIg are considered confidential by the company and cannot be reported here.
- PLEX was not included in any NMAs, so the odds ratio for PLEX was informed by the 57% responder rate for PLEX from the Barth et al. study.

  The EAG noted that the company's response rate for its refractory standard care (see section 3.5) was the same as its referent response rate, which was calculated based on the average placebo response rate across studies identified in the bivariate NMA. During the second committee meeting, the company explained this was because it does not consider the 'basket' of standard care as the comparator for zilucoplan, but only as subsequent treatment. The EAG considered that the company's approach was clinically implausible. This is because people having refractory standard care after first-line treatment includes those having IVIg and PLEX, but that the company's referent response rate implies that there is no treatment benefit for IVIg and PLEX over placebo.

  In the absence of evidence and robust data, the EAG used the company's estimates of response rates for zilucoplan, IVIg and PLEX, as well as the referent response rate. It also used the referent response rate estimate to calculate the response rate for the 'basket' of standard care as subsequent treatment (which the company referred to as refractory standard care; see section 3.5) and included IVIg and PLEX,

which it preferred. Its calculation took into account the revised proportions of people having IVIg (56.7%), PLEX (18.9%), and corticosteroids and or NSISTs (24.4%) in the 'basket' of standard care as informed by the revised EAMS cohort. This resulted in a higher overall referent response rate than the company had assumed. The EAG's preferred response rate for this refractory standard care (including IVIg and PLEX) is considered confidential by the company and cannot be reported here.

The committee recalled its discussion on the uncertainties from the NMAs, including the bivariate NMA, and the requested analyses (see section 3.11). It considered that there are uncertainties in the company's response rates of zilucoplan and IVIg because of the uncertainties from the bivariate NMA (including the non-adjustment of the differential placebo response rates across studies). It also considered there are uncertainties in the response rate for PLEX (because PLEX is not included in any NMA) and so the effectiveness of zilucoplan compared with PLEX remains unclear. There is also uncertainty about the revised proportion of people having the 'basket' of standard care based on the EAMS cohort (see section 3.5) when estimating the response rate for refractory standard care. But it noted that the EAG's approach was also originally based on the company's referent response rate. And this same referent response rate was also used to inform the EAG's estimation of response rates for zilucoplan, IVIg and PLEX. The EAG explained that while the company did attempt to address placebo heterogeneity by using this referent response rate, it would be more appropriate to address placebo heterogeneity through the bivariate NMA directly. The committee agreed that it had not been presented with accurate estimates of treatment response for any of the treatments. It concluded that it would like to see:

- revised response rates informed by NMAs that explore the inclusion of studies on PLEX (including Barth et al.)

- placebo response and baseline population heterogeneities across studies adjusted for in the analysis.

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.

Treatment duration and stopping rule

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 concluded it 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.

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 (see section 3.31).

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 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 company suggested that the EQ-5D may not be sensitive enough to measure the utility impact of corticosteroid use. 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. It considered that there are uncertainties in both the company's and EAG's assumptions and preferred to account for utility decrement associated with corticosteroid use qualitatively in 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 concluded 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.

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 significant 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 company 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 concluded that it would like to see the costs from Lee et al. explored and the company agreed to use these in future analyses.

Use of IVIg and SCIg

3.25 The company's original model assumed that 50% or 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 section 3.6) and the definition of refractory in EAMS (see section 3.6)
- the target population for zilucoplan (see section 3.3)
- the appropriate proportions of people having IVIg, PLEX and NSISTs in the 'basket' of standard care treatments (which the company referred to as 'refractory standard care'; see section 3.4, section 3.5 and section 3.6)
- the comparative effectiveness of zilucoplan is highly uncertain, and that uncertainty is not reflected in the model (see section 3.11 and section 3.16)
- how MSE was implemented in the model; and the uncertainty around how MSE affects the transition probabilities in the model, as well as the proportion of people reaching MSE on zilucoplan, IVIg, PLEX, and corticosteroids and NSISTs (see section 3.13)
- the model does not adequately account for subsequent treatments in terms of sequencing, costs and benefits (see section 3.14)
- treatment response rates used in the model (see section 3.15) and that the uncertainties from the NMAs were not incorporated
- the company's assumed extra utility decrement associated with corticosteroid use in the model (see section 3.20)
- the company's assumed utility increment associated with self-administration of zilucoplan in the model (see section 3.21)
- the extra costs associated with corticosteroid use in the model (see section 3.24).

Committee's preferred assumptions

3.27 The committee's preferred assumptions included:

- The comparators should be modelled as a 'basket' of standard care, with some people having IVIg, some having PLEX, and some having neither. Everyone should have corticosteroids and NSISTs (see sections 3.4 to 3.6).

- The results of the whole trial populations of RAISE and RAISE-XT can be generalised to the NHS population (see sections 3.7 to 3.9).
- Neither the company's nor the EAG's methods of estimating MG-ADL response were satisfactory. The committee would prefer an indirect comparison that incorporates data from all available studies, includes IVIg and PLEX, and directly adjusts for the placebo response. Also, any uncertainty from indirect comparisons should be incorporated in the model (see sections 3.10 and 3.11 and section 3.15).
- It might be reasonable to consider MSE but there are high uncertainties (see section 3.13).
- Subsequent treatment should account for both costs and benefits (see section 3.14).
- The response assessment timepoint should be 3 weeks for all treatments (see section 3.17).
- Additional utility decrement associated with corticosteroid use should be excluded from the model and the committee will take this into account qualitatively (see section 3.20).
- Utility benefits associated with self-administration of zilucoplan should be excluded from the model and modelled as utility decrement associated with IVIg and or PLEX use (see section 3.21).
- Carer disutility should be excluded from the model and the committee will take this into account qualitatively (see section 3.22).
- Costs of IVIg and PLEX should be applied every 4 weeks, and the NHS reference cost should be used for PLEX administration (see section 3.23).
- Assumed use of IVIg should be 100% (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 base-case incremental cost-effectiveness ratios (ICERs) 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 was unable to state an acceptable ICER threshold until the uncertainties have been addressed (see section 3.26).

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. Sex is a protected characteristic under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not a potential equality issue.

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. In response to the first draft guidance consultation, the company presented several analyses for uncaptured benefits (see sections 3.20 to 3.22). 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). It also considered that accounting for utility decrement associated with IVIg and PLEX is more appropriate compared with a utility increment associated with self-administration of zilucoplan (see section 3.21).

Additional analyses

3.32 The committee requests that the company provides the following:

- clarification on the target population for zilucoplan (see section 3.3 and section 3.6)
- an indirect treatment comparison that (see section 3.11):
  - uses data from more of the identified studies
  - includes IVIg and PLEX
  - considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness
  - accounts and adjusts for the differential placebo response and baseline population heterogeneity observed in the trials
  - explores linking the networks by using IVIg as the common comparator to include PLEX
  - respects randomisation.
- statistical codes for any NMAs conducted (these must be submitted for verification)

- information and justification to support its use of a revised EAMS cohort to inform its preferred refractory standard care treatments (see sections 3.4 to 3.6)
- information and justification for MSE including (see section 3.13):
  - sources of data for MSE and information on how MSE was implemented in the model, particularly its effect on transition probabilities
  - additional evidence on the estimation of the proportion of people on zilucoplan reaching MSE
  - further details and justifications for its assumptions on the proportion of people on IVIg and or PLEX, and proportion of people on refractory standard care treatment reaching MSE in the model
  - evidence on the proportion of people in the RAISE placebo arm reaching MSE
  - further details and justification for MSE enduring through the lifetime of the economic model.
- Additional modelling and information on subsequent treatments (see section 3.14), including:
  - modelling of subsequent treatments that includes both the costs and benefits associated with subsequent treatment
  - information on the routine practice for subsequent treatment in the NHS
  - analysis on the proportions of people with refractory gMG who have IVIg and PLEX after IVIg; those who have IVIg and PLEX after PLEX, and those who have corticosteroids and or NSISTs only after IVIg or PLEX.
- revised treatment response rates (see section 3.15) informed by NMAs that explore the inclusion of studies on PLEX (including Barth et al.), and with placebo response heterogeneities and baseline population heterogeneities across studies adjusted for in the analysis
- analysis for utility decrement associated with IVIg and PLEX (see section 3.21)

- analysis that explores corticosteroid costs from the Lee et al. study (see section 3.24)
- scenario analyses that explore a range of time on treatment assumptions (see section 3.18).

Conclusion

Recommendation

3.33 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 analyses. 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 zilucoplan could not be recommended for treating refractory antibody-positive gMG in adults.

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 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.

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