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Draft guidance consultation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: July 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using zilucoplan in the NHS in England.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: 25 July 2024
- Second evaluation committee meeting: to be confirmed
- 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, 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 intravenous immunoglobulin and plasma exchange, so it is unclear how well it works compared with these treatments.

As well as the uncertainties in the clinical evidence, there are uncertainties in the economic model and the cost-effectiveness estimates for zilucoplan. The most likely estimates are substantially above what NICE considers an acceptable use of NHS resources. So, zilucoplan is not recommended.

Issue date: July 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 are needed for 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 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 are associated with notable side effects and that they aim to use minimal effective doses to reduce these. The ABN guidelines recommend non-steroidal immunosuppressants such as azathioprine if remission is not achieved on corticosteroids alone. If there is insufficient response to immunosuppressants or people experience notable side effects on increasing corticosteroid doses, expert advice should be sought on the use of 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 also considers rituximab, an anti-B-cell monoclonal antibody treatment, to be equally effective to IVIg. It has stated that rituximab should 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 other 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 therapy 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 approval).

The clinical experts considered that these criteria broadly describe the population that zilucoplan would be used for in the NHS. The committee noted that in the RAISE clinical trial (see section 3.5), refractory criteria also included that people had to be on 1 year or more of standard treatment. 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 with the clinical experts that the

population defined in the company submission was similar to the population that would have zilucoplan in the NHS.

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: efgartigimod, IVIg and PLEX, excluding corticosteroids and non-steroidal immunosuppressants. At the time of the first committee 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 on the substantial variation in access to IVIg and PLEX 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, there would be some people who instead 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 would 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 comparable to the population who would have zilucoplan in the NHS. The EAMS cohort included 48 people with refractory gMG in the NHS. 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.

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 agreed with the EAG that corticosteroids and immunosuppressants should be included in both arms. The committee also agreed that the efgartigimod EAMS population was sufficiently similar to the zilucoplan target population, and that the proportions of people having each treatment could be taken from the EAMS population.

Clinical effectiveness

RAISE

3.5 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 (a higher MG-ADL score shows more severe symptoms). From baseline to week 12, people who had zilucoplan had a

statistically 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, statistically 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 showed 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

3.6 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

3.7 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 3.8), only RAISE had a pre-defined 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 approximated the refractory population in the NHS who would be considered for IVIg or PLEX. The clinical experts at the 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

3.8 The company did NMAs to estimate the comparative effectiveness of zilucoplan with the comparators. NMAs were done 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 included 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 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, 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 matching-adjusted indirect comparison would be limited by heterogeneity in reporting across trials and by small sample sizes after population matching.

The committee noted that there were several IVIg and PLEX studies that 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. One method that the committee thought could be useful was multivariate NMA in which the

relationship between outcomes can be used to impute relative effect estimates for missing outcomes. A second method suggested by the committee would be to do an NMA of standardised mean differences for MG-ADL and other outcomes, from which odds ratios could then be approximated. The committee concluded that there were multiple issues with the NMA that meant that the comparative effectiveness of zilucoplan was highly uncertain. So, the committee asked the company to provide additional analyses to improve the indirect comparisons and provide scenarios using all relevant evidence.

Economic model

Company's modelling approach

3.9 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 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 52.5 years. The committee concluded that the model could be appropriate for decision making if it accounted for subsequent treatment use (see section 3.10).

Subsequent treatments

3.10 Over time, people in the model return to the 'uncontrolled' health state, and only have corticosteroids and immunosuppressants. The model does

not account for any future use of IVIg or PLEX for people who stop either zilucoplan or the comparators. 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. The clinical experts noted that they would consider IVIg or PLEX for people who stop zilucoplan. They 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 concluded that it would like to see the company account for subsequent treatments in the model.

Treatment response rates

3.11 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 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 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. 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%, 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. 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 concluded 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 concluded that it had not been presented with accurate estimates of treatment response for any of the treatments. It asked the company to provide more analyses to clarify this.

Response assessment timepoint

3.12 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.

Utility values

3.13 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 model also did not apply disutilities for caregiver burden. The EAG noted that the company's approach for modelling utilities was appropriate. The committee thought that there were several uncaptured benefits associated with zilucoplan and asked the company to provide scenarios that consider these (see section 3.19).

Costs

Resource use

3.14 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.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.15 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

3.16 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 level of uncertainty, specifically that:

- the model does not account for subsequent treatments (see section 3.10)
- the comparative effectiveness of zilucoplan is highly uncertain, and that uncertainty is not reflected in the model (see section 3.8 and section 3.11)

- there are uncaptured benefits of zilucoplan that the committee would like the company to try to account for (see section 3.13 and section 3.19).

The committee was unwilling to state an acceptable ICER threshold until these uncertainties are addressed.

The committee's preferred assumptions

3.17 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. All people should have corticosteroids and immunosuppressants. Efgartigimod should not be included as a comparator (see section 3.4).
- The results of the whole trial populations of RAISE and RAISE-XT can be generalised to the NHS population (see sections 3.5 to 3.7).
- 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 adjusts for the placebo response. Also, any uncertainty from indirect comparisons should be incorporated in the model (see section 3.8 and section 3.11).
- The response assessment timepoint should be 3 weeks for all treatments (see section 3.12).
- There are uncaptured benefits of zilucoplan that may affect the utility of people who have it. The committee would prefer the company to present scenario analyses incorporating some of these uncaptured benefits in the modelling (see section 3.13 and section 3.19).
- Costs of IVIg and PLEX should be applied every 4 weeks, and the NHS reference cost should be used for PLEX administration (see section 3.14).

Other factors

Equality

3.18 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

3.19 The committee considered if zilucoplan was innovative. 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 adverse effects. Both patient and clinical experts considered zilucoplan to have advantages for patients, carers, and healthcare professionals. But the committee noted that similar QALYs were generated by each treatment in the model. The committee therefore concluded that there were benefits of zilucoplan that were uncaptured in the modelling. The committee asked the company to present scenario analyses that account for some of these benefits.

Additional analyses

3.20 The committee would like the company to provide the following analyses:

- an improved indirect treatment comparison that:
  - 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 observed in the trials
  - respects randomisation.
- including subsequent IVIg and PLEX in the modelling and the effect on the cost-effectiveness estimates
- scenario analyses incorporating some of the uncaptured benefits of zilucoplan.

Conclusion

Recommendation

3.21 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 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.

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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

Technical lead

Eleanor Donegan and Yelan Guo

Technical advisers

Jeremy Powell

Project manager

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